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Hepatitis B Antigen and Antibody in Patients with Leprosy : A Study of Three Resettlement Villages in Thailand

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SUMMARY **It remains uncertain whether the cellular immune abnormalities of patients with lepromatous leprosy interfere with resolution of hepatitis B virus (HBV) infections. To investigate this question in an area coendemic for the two diseases, we determined the prevalence of hepatitis B surface antigen (HBsAg) and antibody (anti-HBs) in: 1) 204 leprosy patients living in three leprosy resettlement villages; 2) 198 contacts living in the same villages; and 3) 44 newly diagnosed leprosy patients in Thailand. Within the villages, the prevalence of HBsAg positivity was inversely related to age, tended to be more frequent in patients with tuberculoid than lepromatous leprosy, and was similar after age adjustment among persons with and without leprosy. The prevalence of HBV markers found in newly diagnosed patients was similar to that in the villagers. We conclude that extensive HBV transmission had occurred in the resettlement villages and that the natural history of HBV infection was similar in persons with, whether tuberculoid or lepromatous, and without leprosy.**

In 1967, Blumberg and his associates first reported finding the "Australia antigen" more frequently in the sera of patients with lepromatous leprosy than in either patients with tuberculoid leprosy or healthy control subjects from the same area.[1] The authors recognized that the differences in seroprevalence might be due to more frequent institutionalization of the lepromatous than the tuberculoid patients included in their study. Since that initial report, conflicting data on the relationship between leprosy and hepatitis B virus infection have been published.[2] Some have reported higher HBsAg carrier rates in patients with lepromatous leprosy.[1,3,4] Others have not found this relationship.[5-10] It is now recognized that several factors may influence the relationship between HBsAg carrier rates and leprosy. Among them are differences between leprosy patients and controls in their age, socioeconomic status, frequency of exposure to HBV, contact with hospitals or health care institutions, and general immunocompetence of those with leprosy in clearing an HBV infection after exposure. It has become clear that a study of the relationship of HBV and leprosy must include sensitive assays of HBV infection (both HBsAg and anti-HBs) and comparable exposure to HBV of all study groups before one can conclude that the depressed immune status or genetic factors associated with lepromatous leprosy can explain any association detected.

Since both *Mycobacterium leprae* and HBV infections are coendemic in many regions of the world, it is both important and feasible to determine whether the abnormalities of cellular immunity found in leprosy,[11-13] various aspects of the diagnosis or treatment of leprosy, or genetic factors associated with leprosy susceptibility, increase the rates of HBV infection, or of HBsAg carriage once infection with HBV has occurred.

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In Thailand, resettlement villages had been established for the purpose of isolating leprosy patients from those without disease, to provide them specialized medical and occupational care, and for their rehabilitation. At present, these villages consist of individuals who have a history of leprosy and others who have not had leprosy. The three resettlement villages included in this study were located in isolated rural areas in northern Thailand and were similar to each other. The residents were generally quite poor but derived a limited income from selling handicrafts through commercial or missionary outlets. They raised small amounts of such food crops as rice, peanuts, fruits and vegetables. They had infrequent contact with hospitals or other health care institutions.

In order to determine whether people with lepromatous leprosy have increased susceptibility to, and/or less capacity to resolve, an HBV infection we determined the prevalence of HBsAg and anti-HBs in the following groups: 1) the residents of three resettlement villages who had a diagnosis or history of leprosy; 2) the residents of these villages who had no history of leprosy; and 3) a group of newly diagnosed leprosy patients.

MATERIALS AND METHODS

As part of the Chiang Mai/Illinois Leprosy Research Project, epidemiological surveys were carried out in three leprosy resettlement villages (Chiang Dao, Lii and Mae Soon) situated in northern Thailand. In addition to demographic and general medical surveys performed in each village, all residents were examined by an experienced leprologist (T.C.S.). Clinic charts from the McKean Rehabilitation Center (a leprosy treatment center located in Chiang Mai) were reviewed as part of the patient evaluation. For the purpose of this analysis patients were classified according to the type of leprosy present at the time of active disease. A group of newly diagnosed leprosy patients were also entered into the study at the time of their initial diagnosis at McKean, prior to the initiation of anti-leprosy chemotherapy. All leprosy patients were classified using the five-group system described by Ridley and Jopling.[14] Surveys were carried out in 1982 and 1983 at which time no HBV vaccine had been used in the study villages. Among the newly diagnosed patients, HBV immunization histories were not recorded. (Since HBV vaccination was not freely available in Thailand in 1982-3 and most of the study patients were poor, we consider it unlikely that these subjects would have received HBV vaccination prior to our assessment.)

Blood was drawn from villagers over the age of six years who volunteered for the study. Sera were separated and frozen at -70° C in Chiang Mai, shipped on dry ice to the USA, where they were stored at -70° C until tested. Specimens were assayed for the presence of HBsAg and anti-HBs employing standard radio-immunoassays (Ausria II, Ausab; Abbott Laboratories, North Chicago, IL) at either the University of Illinois or the Centers for Disease Control, Phoenix, Arizona.

For this analysis patients with leprosy were grouped as having either tuberculoid (TT, BT) or lepromatous (BB, BL, LL) disease. Proportions were compared by constructing 2 × 2 tables and assessing significance with either the chi-square or Fisher's exact test. The prevalence of hepatitis markers among leprosy patients and their contacts in the resettlement villages were compared before and after the data were age-adjusted to the age distribution of the population of Thailand reported in the 1980 census.[15] The direct method of age-adjustment was used for this comparison.

RESULTS

HBV serology was carried out on sera from three groups of northern Thai subjects: residents with leprosy from three leprosy resettlement villages, fellow residents without leprosy, and people with newly diagnosed leprosy. In the villages, 204 (51%) of the 402 residents surveyed had leprosy (Table 1). The prevalence of leprosy increased with age from 5 percent in those less than 30 years old to 88 percent in villagers who were 50 years or older. The type of leprosy was evenly distributed, with 102 tuberculoid (TT, BT) and 102 lepromatous (BB, BL, LL) patients. Serologic markers of HBV infection were found in 78 percent of the residents of these villages (Table 2). Of those with HBV markers, 18 percent

Table 1. Prevalence of leprosy by disease type and age in residents of three leprosy resettlement villages in northern Thailand

Age (years)	n	Tuberculoid # (%)	Lepromatous # (%)	No leprosy # (%)
0–9	18	0 (0)	0 (0)	18 (100)
10–19	67	2 (3)	0 (0)	65 (97)
20–29	67	3 (4)	2 (3)	62 (93)
30–39	68	27 (40)	18 (26)	23 (34)
40–49	69	22 (32)	31 (45)	16 (23)
50–59	62	27 (44)	30 (48)	5 (8)
⩾ 60	51	21 (41)	21 (41)	9 (18)
Total	402	102 (25)	102 (25)	198 (49)

(57 of 313) were positive for HBsAg. Serological markers were present slightly but significantly more frequently among individuals with leprosy (169 of 204, 82.8%) than among residents with no history of leprosy (144 of 198, 72.7%; chi-square = 5.39, P = 0.02). After age-adjustment, there was no significant difference in HBV markers between those with (69.3%) and without (66.8%) a history of leprosy. Although the prevalence of these markers did not differ with leprosy type (84 of 102 tuberculoid *vs* 85 of 102 lepromatous), there was a tendency for HBsAg positivity among those with hepatitis markers to occur more commonly in residents with tuberculoid than in those with lepromatous disease (15 of 84 *vs* 6 of 85, respectively; P = 0.06).

The prevalence of HBV infection and HBsAg positivity is shown by age in Table 2. It appears that most HBV infections occurred during the first two decades of life. HBsAg positivity was highest in those 10 to 19 years of age and decreased with age thereafter. Of those residents with HBV markers, the frequency of HBsAg positivity decreased significantly from 25 percent (41 of 165) among those less than 40 years of age to 11 percent (16 of 148) among those older than 40 years (P = 0.002).

Forty-four newly diagnosed leprosy patients were also studied for their HBV status. They ranged in age from the second to seventh decade (Table 3). Serologic markers of HBV infection were detected in 36 (82%) of these patients and 8 (22%) of this infected group were HBsAg positive. In a pattern similar to that found in residents of the resettlement villages, HBV infection was high in all age groups. HBsAg positivity, among those with HBV markers, tended to decrease with age but did not attain statistical significance when age 40 was used as a cut-off (5 of 13, under age 40 *vs* 3 of 23, 40 and over; P = 0.09).

Table 2. Prevalence of leprosy, HBsAg and anti–HBs by age in residents of three leprosy resettlement villages in northern Thailand

Age (years)	n	Leprosy # (%)	HBsAg # (%)	Anti–HBs # (%)	HBV* # (%)	Ag+/HBV** %
0–9	18	0 (0)	1 (6)	6 (33)	7 (39)	14
10–19	67	2 (3)	15 (22)	34 (51)	46 (69)	33
20–29	67	5 (7)	11 (16)	41 (61)	52 (78)	21
30–39	68	45 (66)	14 (21)	50 (74)	60 (88)	23
40–49	69	53 (77)	7 (10)	47 (68)	53 (77)	13
50–59	62	57 (92)	6 (10)	48 (77)	52 (84)	12
⩾60	51	42 (82)	3 (6)	41 (80)	43 (84)	7
Total	402	204 (51)	57 (14)	267 (66)	313 (78)	18

*HBV defined as positive for HBsAg and/or anti–HBs.
**The number of people positive for HBsAg divided by the number of people positive for HBsAg and/or anti–HBs.

Table 3. Prevalence of HBsAg and anti–HBs by age in newly diagnosed leprosy patients in northern Thailand

Age (years)	n	HBsAg # (%)	Anti–HBs # (%)	HBV* # (%)	Ag+/HBV** %
0–9	0	–	–	–	–
10–19	4	2 (50)	1 (25)	3 (75)	67
20–29	10	1 (10)	5 (50)	6 (60)	17
30–39	5	2 (40)	2 (40)	4 (80)	50
40–49	9	2 (22)	8 (89)	9 (100)	22
50–59	12	1 (8)	9 (75)	10 (83)	10
⩾60	4	0 (0)	4 (100)	4 (100)	0
Total	44	8 (18)	29 (66)	36 (82)	22

*HBV defined as positive for HBsAg and/or anti–HBs.
**The number of people positive for HBsAg divided by the number of people positive for HBsAg and/or anti–HBs.

DISCUSSION

The prevalence of HBV infection in the leprosy resettlement villages was found to approach 80 percent with infection occurring frequently in the first decades of life. (Since some HBV-infected individuals, diagnosed on the basis of anti-HBc antibodies, may lack both HBsAg and anti-HBs our findings may underestimate the true prevalence.) For comparison, it has been estimated that the overall prevalence of HBV infection in Thailand is 40-60 percent [16]. Since the prevalence of leprosy was very low among villagers less than 30 years of age, when HBV prevalence had already reached a plateau, we conclude that the occurrence of HBV infection was not directly related to the presence of clinical leprosy in this population.

The results of our studies suggest that the conversion of HBV infection from HBsAg positive to negative was age dependent and leprosy independent. A decreasing prevalence of "Australia antigen" with increasing age was reported in the original report by Blumberg [1] and confirmed by others. [4,7] The recent studies have included sensitive assays of anti-HBs, which have permitted a calculation of the proportion of HBsAg positivity among those HBV infected. This calculation is important because it makes possible the distinction between the

total burden of HBV infection and the proportion of HBsAg carriers among those infected. [3,5]

In lepromatous leprosy, lymphocyte proliferative responses to *M. leprae*-derived antigens are impaired or absent. [12,13] This impairment of antigen-specific responses persists even after apparently effective anti-leprosy treatment. [11] The extent to which these abnormalities of cellular immune response have a non-specific component which includes T-cell help of antibody responses to HBV is uncertain. Even when only studies employing highly sensitive techniques for detection of HBsAg and anti-HBs are considered, it is unclear whether or not leprosy type plays a role in the resolution of HBV. [3,7,8] In this study the proportion of subjects HBsAg positive among all those HBV infected did not differ between patients with tuberculoid and those with lepromatous leprosy. Interestingly, HBsAg positivity actually tended to be somewhat more common among tuberculoid patients. This finding would appear to be the opposite of what one might expect if impaired immune responses in patients with lepromatous leprosy increased their risk of HBsAg carriage after HBV infection. Similar findings have been observed in patients from South Africa [10] but interpretation of our results is further complicated by the slightly younger age of the tuberculoid than lepromatous patients (Table 1).

The differences in the age-specific incidence of hepatitis B virus [17,18] and *M. leprae* [19] infections within a given population or between different populations could explain some of the apparent discrepancies reported on the relationship between these two infections. In many populations where both leprosy and hepatitis are endemic, especially in Asia, HBV infections are frequently acquired at an early age. [18] In contrast, in other populations, especially in Europe and in some African countries, HBV infections occur more commonly at a somewhat older age. [17] Leprosy infections too are often age related; tuberculoid diseases often have onset at a younger age than does lepromatous leprosy. As leprosy begins to disappear from a population the age at onset of new cases often increases and the proportion of the cases which are lepromatous commonly increases. [19,20] Therefore, the point prevalence of HBV infection and the proportion of those HBV infected who are HBsAg carriers among individuals with various types of leprosy and controls could be expected to vary in different populations.

With the availability of effective hepatitis B vaccines for use by national immunization programs, our findings suggest several practical points. First, HBV transmission in poor villages at the fringes (literally or figuratively) of a medical delivery system may be more extensive than is appreciated. Second, the need to begin immunization with hepatitis B vaccine early in life is again reconfirmed. And third, persons with leprosy are no more likely to transmit HBV after infection than other HBV-infected persons; conversely, leprosy patients still susceptible to HBV infection can be expected to produce a normal protective immune response to vaccination.

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REFERENCES

1. Blumberg BS, Melartin L, Lechat M, Guinto RS. Association between lepromatous leprosy and Australia antigen. Lancet 1967; 2 : 173-6.
2. Chiron JP, Denis F, Yvonnet B, Coursaget P, Diop-Mar I, Languillon J. Leprosy and hepatitis B. Acta Leprol (Geneve) 1985; 97 : 169-99.
3. Fakunle YM, Whittle HC. Hepatitis-B virus infection in patients with leprosy: a serological study in a leprosarium in Northern Nigeria. Trans R Soc Trop Med Hyg 1981; 75 : 623-5.
4. Serjeantson S, Woodfield DG. Immune response of leprosy patients to hepatitis B virus. Am J Epidemiol 1978; 107 : 321-7.
5. Gully PR. Prevalence rates of hepatitis B surface antigens in patients with leprosy.Trans R Soc Trop Med Hyg 1982; 76 : 283-4.
6. Kelkar SS, Niphadkar KB, Karc PM, Gharpuray MB. Environment and carriage of hepatitis B antigen in leprosy. Indian J Med Res 1974; 62 : 1794-9.
7. Papaioannou DJ, Kaklamani EP, Parissis NG, Koumantaki IG, Karalis DTh, Trichopoulos DB. Hepatitis B virus (HBV) serum markers in Greek leprosy patients. Int J Lepr Other Mycobact Dis 1986; 54 : 245-51.
8. Patterson F, Baungart K, Britton W, Gallagher N, Bagshawe A. Hepatitis B and leprosy: differential transmission in a village in Papua New Guinea. In : Zuckerman A, ed, Viral hepatitis and liver disease. New York : Alan R Liss, 1988 : 186-9.
9. Shwe T, Zuckerman AJ. Australia antigen and antibody in British patients with leprosy. J Clin Pathol 1972; 25 : 401-2.
10. Sher R, MacKay ME, MacNab GM, Kok SH, Koornhof HJ. Hepatitis B antigen, hepatitis B antibody, and subtypes in leprosy. Infect Immun 1977; 17 : 1-3.
11. Brown AE, Vithayasai V, Scollard DM, *et al.* Lymphocyte transformation in lepromatous leprosy: a study of the influence of disease activity and symptom duration. Southeast Asian J Trop Med Public Health 1986; 17 : 104-10.
12. Faber WR, Leiker DL, Nengerman IM, Zeijlemaker WP, Schellekens PThA. Lymphocyte transformation test in leprosy: decreased lymphocyte reactivity to *Mycobacterium leprae* in lepromatous leprosy with no evidence for a generalized impairment. Infect Immun 1978; 22 : 649-56.

13. Gaylord H, Brennan PJ. Leprosy and the leprosy bacillus: recent developments in characterization of antigens and immunology of the disease. Ann Rev Microbiol 1987; 41 : 645-75.

14. Ridley DS, Jopling WH. Classification of leprosy according to immunity : a five-group system. Int J Lepr Other Mycobact Dis 1966; 34 : 255-73.

15. National Statistical Office, Office of the Prime Minister, Thailand Population and Housing Census 1980, Bangkok, Thailand.

16. Pramoolsinsap C, Pukrittayakamee S, Desakorn V. Hepatitis B problem in Thailand. Southeast Asian J Trop Med Public Health 1986; 17 : 219-28.

17. Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. Lancet 1989; 1 : 889-92.

18. Grossman RA, Benenson MW, Scott RM, Snitbhan R, Top FH, Pantuwatana S. An epidemiologic study of hepatitis B virus in Bangkok, Thailand. Am J Epidemiol 1975; 101 : 144-59.

19. Fine PEM. Leprosy: the epidemiology of a slow bacterium. Epidemiol Rev 1982; 4 : 161-88.

20. Irgens LM. Leprosy in Norway. Lepr Rev 1980; 51 (Suppl. 1) : 1-125.