Subtypes of Australia Antigen in Persistent Australia Antigenemia and Sporadic Hepatitis Among Patients With Lepromatous Leprosy and Their Segregated Children With No Apparent Clinical Illness[1]

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Individuals who develop persistent hepatitis B antigenemia (HBAg) with clinically inapparent hepatitis, or no evidence of hepatitis at all, have been of particular interest because they are potentially infectious and pose a hazard to the general population ([28]). The high carrier rate (2.65%) in normal Indian subjects ([10]) has been associated with a hot climate and poverty ([7]). This might be the cause of the high incidence of post-transfusion hepatitis (18.9%) in Delhi ([13]) due to blood donors who belonged to the poverty stricken element of society. Recently, 32 lepromatous leprosy patients were followed for 2.5 years and a persistent high incidence of HBAg was demonstrated in 8.1% of patients who had no clinical manifestation of hepatitis ([11]). However, HBAg was not found in the sera of 59 tuberculoid cases who lived together with these lepromatous patients. This led to the conclusion that the high incidence and persistence of HBAg in lepromatous leprosy patients was associated with the depressed state of their cellular immunity.

HBAg is known to have several subsidiary surface antigenic specificities ad, ay, ar and aw, which exhibit differences in their geographical distribution and clinical expression of infection ([30]). In Delhi, ad antigen was found predominant amongst professional blood donors as opposed to a higher incidence of ay in the healthy voluntary blood donors, type B viral hepatitis and in cirrhosis ([9]). The present report deals mainly with the subtyping of three determinants ad, ay and ar in the sera of leprosy patients with and without clinical hepatitis and their apparently healthy offspring.

MATERIALS AND METHODS

Blood samples were obtained from leprosy patients and their children by systematic surveillance. Thirty-one percent of the patients were addicted to *Canibis indica* and country liquor. Only patients denying drug addiction and blood transfusion were included in the study.

Human materials and screening of their sera for HBAg. *Leprosy patients.* Sera from 135 biopsy proved cases of lepromatous leprosy, including 25 females with ages ranging from 20 to 60 years, living at two leprosy homes (a leprosy village and one military hospital), were collected and stored at –20°C. All patients were taking standard antileprosy treatments and belonged to a low socioeconomic group. The diagnosis of leprosy was based on clinical examination, lepromin (Dharmendra) test and skin biopsy. The patients were classified on a histopathologic basis ([23]). Only borderline and polar lepromatous cases were included for the present study because mostly their sera contained HBAg ([11]).

Children of leprosy patients. Sera from 113 apparently healthy girls and 43 boys with no clinical or histopathologic leprosy, having a good nutritional status and with ages varying from 4 to 18 years, were screened for HBAg and HBAb. Only one female baby was six months old. During the fourth year of their life, these children had been isolated from their parents and were put on prophylactic treatment; however, they usually stayed with their parents during holidays and festivals.

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Controls. The study had two types of controls: a) 2,982 healthy Indian army personnel with ages varying from 18 to 34 years, having excellent nutritional status, and living in good hygienic conditions were taken as the first control group; b) since most of our patients with lepromatous leprosy were undernourished, a second control group was also included which consisted of 34 chronically starved adults, with ages ranging from 20 to 65 years. They had no clinical leprosy and their nutritional status was assessed according to the criteria described by the WHO ([29]). Thus, they had diminished body weight (35% to 40% lower body weight than Indian standards), a dietary history of low calorie and protein intake, absence of any condition other than undernutrition, low total serum protein level of 4.6 ± 0.44 gm per 100 ml (normal = 6.45 ± 0.45 gm/100 ml) with albumin levels below 2.4 gm% (normal = 3.4 ± 0.21 gm/100 ml) and low urinary creatinine excretion rate of 363 ± 84 per 24 hours against a normal rate of 853 ± 78 per 24 hours. The sera of the above four groups were then screened for HBAg and HBAb by electro-osmodiffusion ([10]).

Subtyping HBAg in the sera of the index cases. The technics of immunodiffusion (ID) and electro-osmodiffusion (EOD) were described by Le Bouvier ([17]) and were subsequently modified by Dutta *et al* ([9]). In the former method, central wells were charged with anti-ad, anti-ay and anti-ar antisera, and the top outer wells with the standard antigens. The other outer five wells were charged with test sera. In the latter method, the subtype antisera were placed in the anode wells while the cathode wells contained test sera. The system was subjected to a constant 200 volts for two hours. The results were read immediately and after 24 hours.

HBAg carriers in families of index cases. As far as possible, first degree relations (siblings and parents) of seven index cases (children carrying HBAg) were located. Their sera were screened for HBAg by EOD, and the positive sera was subsequently subtyped. Also another group of sera from the first degree relatives of ten children, who were not carriers of HBAg, were screened for the virus. This group was used as a control.

Cellular immunity in the lepromatous subjects and their children. Specific cellular immunity against *M. leprae* by intradermal injection of 0.1 ml Dharmendra lepromin as well as general status of cell-mediated immunity against intradermal injection of ten units of old tuberculin, 125 units of streptokinase-streptodornase, and 10^6 heat inactivated vaccinia virus were studied in these subjects following standard methods ([4, 24, 25]). Contact hypersensitivity tests were performed by sensitizing the test subjects with 2,000 microgram dinitrochlorobenzene with subsequent challenge by 50 microgram hapten after 21 days ([24]). All subjects, in whom heat inactivated vaccinia virus was injected intradermally, had primary vaccination and gave a history of revaccination. Children were revaccinated only three months prior to the test. Also, all children in whom the tuberculin test was performed had prior BCG vaccination.

Quantitative estimation of serum immunoglobulins and complement. Serum immunoglobulin G, A and M along with complement C3 were estimated using the single radial immunodiffusion technic ([18]) to note any difference between the levels of immunoglobulin and complement in HBAg positive and negative subjects.

RESULTS

Incidence and persistence of HBAg and occasional hepatitis among leprosy patients. Table 1 illustrates the incidence and persistence of HBAg in patients with lepromatous leprosy and their children. The carrier rates of HBAg in the lepromatous leprosy patients (10.3%) and their children (9.6%) were comparable, and were much higher than that observed in the control group of soldiers (2.28%) and in the 34 undernourished subjects (2.9%). The two control groups had comparable HBAg carrier rates although with respect to their socio-economic, nutritional and immunologic status (Table 5); these two groups were poles apart. The incidence of HBAg among these children was age dependent, because among 15 HBAg positive children, only two were below six years, six were between seven and ten years, and seven were between eleven and eighteen years. But sex does not seem to have any relation to the prevalence of HBAg among these children or among the leprosy patients. Thus, of 25 female lepromatous cases, only two (8.0%) had HBAg.

TABLE 1. *Incidence and persistence of HBAg among lepromatous leprosy patients and their apparently healthy children.*

Groups	Subjects screened	Electroimmunodiffusion test	
		Australia antigen number (%)	Australia antibody number (%)
Lepromatous leprosy	135	14 (10.3)	1 (0.74)
Children of patients with leprosy:	156	15 (9.6)	2 (1.2)
Girls	113	11 (9.7)	1 (0.88)
Boys	43	4 (9.5)	1 (2.33)
Controls:			
Healthy soldiers	2,982	68 (2.28)	3 (0.1)
Severely undernourished adults	34	1 (2.9)	1 (2.9)

Eleven of fifteen children with HBAg could be followed and were found to be asymptomatic carriers for at least two years. Similar follow-up study was possible in only two lepromatous patients who were carriers of HBAg for four years and had no clinical manifestations of hepatitis during this period. Three lepromatous cases, including one female, had developed icteric hepatitis when HBAg was detected in the sera of the two male patients for the first time. It is not known whether they were its carrier before they developed clinical disease. One male patient was the father of one carrier child. The female case with hepatitis was the mother of another carrier girl. But HBAg could not be demonstrated in her serum although she had high levels of serum bilirubin and transaminases. Another female case with lepromatous leprosy and severe reaction, who developed fatal renal failure and terminal bronchopneumonia, also showed HBAg in her serum. Besides these three HBAg positive cases, all other 26 subjects carried HBAg without any clinical or biochemical evidence of hepatitis. Interestingly, the incidence of HB antibody was higher among leprosy patients, their children and undernourished subjects than among soldiers (Table 1).

Subtypes of HBAg. Table 2 presents the subtypes of HBAg. Two male patients, who developed icteric hepatitis, and one female case who died of renal failure, showed ay subtype only. One serum did not give any reaction with anti-ad, anti-ay or with anti-ar antisera. This untypable serum may have had a low titer of virus. The frequencies of ad and ay subtypes among the leprosy patients and their children were comparable and ay subtype was predominantly present in both

TABLE 2. *Australia antigen subtypes in leprosy patients and their children.*

Groups	Total no. HBAg positive sera selected by screening test	Subtype of Au antigen				
		Number and (%) of distribution				
		ad	ay	ar	ady	untyped
Lepromatous leprosy	15	3 (20)	11 (73)	nil	2 (13)	1 (6.6)
Children of leprosy patients	14	2 (14.3)	11 (78.6)	1 (7.1)	nil	nil
Controls:						
Healthy soldiers	22	8 (36.4)	13 (59.1)	not done	1 (4.5)	nil
Severely undernourished adults	1	nil	1	nil	nil	nil

TABLE 3. *Mean levels of serum bilirubin and transaminases in two lepromatous leprosy patients who developed icteric hepatitis and showed HBAg in their sera.*

Clinical data and laboratory values	First test	Second test
	At peak of illness	105 days after first test
Jaundice	+	–
Mean serum bilirubin (mg per 100 ml)	5.3	0.5
Mean serum SGOT (units per ml)	90	60
Mean serum SGPT (units per ml)	128	50
HBAg antigenemia	+	+
Subtype of HBAg	ay	ay

groups. Thirteen HBAg positive serum samples, including 11 from children and 2 from leprosy patients, were followed for two to four years and their subtypes were found to remain unchanged during the course of this period.

Serum bilirubin and transaminases in icteric hepatitis. Table 3 depicts the levels of serum bilirubin and transaminases at the height of clinical illness and 105 days thereafter in two lepromatous leprosy cases having hepatitis. Though their clinical levels of serum bilirubin, SGOT and SGPT declined considerably and their clinical jaundice disappeared, HBAg of ay subtype persisted for more than three months. No difference between the levels of serum bilirubin and SGOT was observed among asymptomatic subjects with or without HBAg (Table 4). However, the levels of SGPT were higher in carriers than in those who had no HBAg in their sera, although these levels were within normal limits in both groups (Table 4).

Cellular immune response in leprosy patients and their children. Of 132 children there were only 13 (10%) children who did not respond to old tuberculin, but showed positive early lepromin reaction which suggested that these children were infected with lepra bacilli ([20]). However, 37.2% of the children responded to tuberculin and also gave an early lepromin reaction which probably indicated that cross-reactive antigens were present in the environment. Table 5 clearly indicates that, in comparison to the normals, there was spectacular depression of cellular immunity in the subjects with severe undernutrition, in patients with lepromatous leprosy, and also, to a lesser extent, in the children of the leprosy patients. In lepromatous leprosy specific anergy towards *M. leprae* was invariably present in all cases and general unresponsiveness towards previously encountered antigens was also found in some cases. Some patients were incapable of responding to DNCB, a new antigen titer. Within the group of children, the proportion of positive late lepromin responders was significantly lower in the children with HBAg (17%) than in those without it (35%). Also no child with HBAg showed 3+ or 4+ reactions to DNCB challenge, although 20% of the children without it showed such heightened response. These data indicate that the carriers of HBAg were more unresponsive to delayed reactions than those without it.

The data for the skin tests in 33 children in whom all the five tests were possible were analyzed. Table 6 illustrates that most children who were nonreactive to multiple antigenic challenges did not show positive late lepromin reaction and thus they had poorer resistance against *M. leprae*. This table further shows that 33% of children with HBAg were anergic to multiple antigens; on the other hand, only 7.4% of children without HBAg

TABLE 4. *Mean level of serum bilirubin and transaminases in leprosy cases and their children with or without HBAg. No clinical hepatitis.*

Laboratory values	HBAg positive (9)	HBAg negative (23)	t value
Serum bilirubin	0.2 ± 0.1	0.25 ± 0.1	
SGOT	10.1 ± 3.4	14.8 ± 9.9	2.0
SGPT	16.8 ± 1.7	9.2 ± 3.5	8.4

TABLE 5. *Assessment of cellular immunity by* in vivo *tests. Impaired delayed hypersensitivity reactions in lepromatous leprosy patients and their apparently healthy children.*

Intradermal or contact delayed hypersensitivity	Groups of subjects			
	Controls			
	Normal soldiers (15)[a]	Severely undernourished adults (34)[a]	Lepromatous leprosy patients (16)[a]	Children of leprosy affected subjects
0.1 ml lepromin (Dharmendra)				
early reaction, % +	22	nd[b]	0	32 (97)[a]
late reaction, %+	80	nd	0	32 (82)
10 TU O.T., % +	100	16	25	56 (85)
100 TU in nonresponders to 10 TU, % +	—	95	44	nd
125 U streptokinase-streptodornase, % +	80	10	14	65 (71)
Contact 2:4 dinitrochlorobenzene, % +	100	10	29	88 (43)
1 million heat inactivated vaccinia virus in 0.1 ml buffer, mean induration in mm with s.d.[c]	14.6 ± 3.8	0.8 ± 1.4	5.4 ± 5.3	7.5 ± 2.4 (46)

[a] Figures in parentheses indicate number of subjects tested.
[b] nd = not done.
[c] s.d. = standard deviation.

TABLE 6. *Relation of late lepromin (Mitsuda) reaction with the various skin tests in children of leprosy affected patients.*

Positive response to	Children[a]		Positive late lepromin reaction in children	
	Number	%	Number	%
All 5 antigens[b]	5	15	4	80
Any 4 antigens	13	39	8	61
Any 3 antigens	11	33	2	18
Only 2 antigens	4[c]	12	nil	0

[a] Total number of children was 33: 27 were without HBAg and 6 were carriers.
[b] All 33 children of leprosy affected subjects were tested for delayed hypersensitivity towards following five antigens: old tuberculin, streptokinase, DNCB, heated inactivated vaccinia virus and Dharmendra lepromin (early reaction). The incidence of positive late lepromin reaction was higher in those children who responded to all antigens and declined remarkably in those who were reactive to fewer antigens. This indicated that children having generalized immunologic anergy had poor resistance against leprosy.
[c] Of 4 children, 2 had HBAg. Thus 2 of 6 (33%) children with HBAg and 2 of 27 (7.4%) children without it showed nonreactivity to multiple antigens.

TABLE 7. *Levels of serum immunoglobulins and C3 complement in L patients and their children with or without HBAg.*

Type of subjects	Australia antigenemia	No. of subjects	Mean serum immunoglobulin level			Mean serum complement level
			IgG	IgA	IgM	C3
			mg per 100 ml ± s.d.[a]			mg per 100 ml ± s.d.
Lepromatous leprosy	yes	10	1267 ± 244	406 ± 154	190 ± 80	173 ± 68
	no	20	1149 ± 187	225 ± 114	153 ± 28	110 ± 34
t value			1.34	3.37	1.42	2.74
Apparently healthy children of leprosy patients	yes	10	1121 ± 216	208 ± 49	154 ± 57	250 ± 104
	no	20	1170 ± 104	149 ± 70	169 ± 84	200 ± 28
t value			0.60	2.70	0.60	1.49

[a] s.d. = standard deviation.

were nonreactive to many antigens. These data therefore indicate that the carriage of HBAg was associated with generalized impairment of cellular immunity and poor resistance against leprosy.

Serum immunoglobulin and complement levels. Table 7 shows that within the leprosy group, the patients carrying HBAg had significantly higher mean levels of IgA and C3 complement than those who were not carriers, but no such significant difference was observed in the children although the levels of IgA and C3 were raised in HBAg carrier children. Recently, it has been demonstrated that the immunoglobulins in infants with hepatitis associated with HBAg may be elevated ([16]). None of the children in our series had hepatitis although they were carriers of HBAg.

Incidence of HBAg and their subtypes in the family with and without HBAg. We were able to trace the incidence of HBAg in the first degree relations within the families of seven index cases (Fig. 1). It was possible to screen the sera of 15 siblings and 11 parents of these index children. Four siblings of four different index carrier children and two fathers of two index cases showed HBAg in their sera. All these subjects lived separately in different institutions. Furthermore, these four siblings had no clinical leprosy or hepatitis but their fathers were suffering from lepromatous leprosy associated with *erythema nodosum leprosum* and severe icteric hepatitis. The subtypes in the index cases are similar to those in their families, but they are not invariably identical. A lepromatous mother of another index case developed icteric hepatitis, but HBAg could not be demonstrated in her serum. Thus, among 26 family members of the seven index cases, seven subjects (27%) either showed HBAg or had hepatitis. In the control group, similar screening for HBAg in the families of 12 children of leprous parents who were not carriers of hepatitis associated virus, revealed that none of their 12 siblings and 14 parents carried HBAg in their sera.

DISCUSSION

Associations of high carrier rate of HBAg. Increased incidence of HBAg in the patients with lepromatous leprosy has been attributed to their impaired cellular immunity ([6, 11]). This was recently criticized by Godal *et al* ([14]), who associated high carrier rate of HBAg with institutionalization. But the absence of HBAg in 59 patients with tuberculoid leprosy, living in the same institution together with the patients of lepromatous leprosy with high carriage rate as observed earlier ([11]) and the present observation of low carrier rates in soldiers as well as in undernourished subjects both living in institutions, does not support the notion of the association of institutionalization with high carriage rate of HBAg. Further, this concept also does not explain the smaller number of late lepromin reactors and DNCB responders among children with HBAg as compared with those without it (Table 5). Thus, it is possible that the high carrier rate of virus B hepatitis in these children was related to the inherent host-parasite interrelationships.

Immunologic deficiency predisposes to the development of HBAg carrier state ([27]). This formulation is also in keeping with our ob-

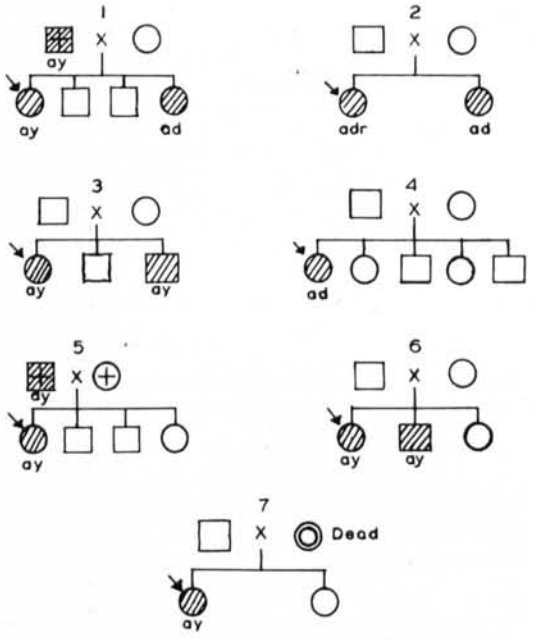

FIG. 1. Clustering of HBAg of various subspecificities in the families of leprosy-affected subjects. Shaded areas show individuals (carriers) who had HBAg in their sera. Blank areas show individuals who were not carriers of HBAg. Arrows show index cases (healthy daughters of leprosy-affected subjects) carrying HBAg. Plus signs show cases with icteric hepatitis. In family 5, the father had clinical jaundice and carried HBAg in his serum. The mother also had clinical jaundice, but HBAg could not be detected in her serum samples. It should be emphasized that the parents, their daughters and sons were all living in separate institutions.

served high carriage rate in the children of leprosy patients because they also had some deficit of cellular immunity against a wide variety of antigens (Tables 5, 6). This is similar to the observations of Agarwal and Sutnick (1) who found impairment of lymphocytic functions in children with Down's syndrome even without HBAg, and claimed that PHA hyporesponsiveness in patients with Down's syndrome might probably be inherited. It is difficult to say at the present whether the observed impairment of cellular immunity in our child subjects is primary or acquired, because subclinical infection of the children of leprosy patients with *M. leprae* in their early life could cause suppression of their immune response (14) and bring about a decrease in host resistance, thus facilitating high HBAg carrier rates. Evidence of subclinical infection with *M. leprae* in the partially segregated children, born of leprosy affected subjects, might be derived from positive early lepromin reaction in tuberculin negative children (20). There were at least 13 (10%) such children in our present series. This low proportion of responders found among the contacts of active lepromatous patients, though it appeared paradoxical, was not unexpected because close contacts with lepromatous patients often converted individuals into lepromin nonresponders (14).

As far as we know, the high incidence of HBAg in the apparently healthy offspring of leprosy affected parents has been reported for the first time. A recent study has shown a high proportion of infants with neonatal hepatitis associated with HBAg in Greece, which was attributed to the high prevalence of HBAg carriers in that country, transmitting the virus to infants during or after birth (16). It is of interest that the incidence of HBAg in patients with lepromatous leprosy and with leukemia in Brazil, where the antigen is not common in the general population, is low (31). We, therefore, suggest that the high incidence of HBAg in the children of leprosy affected subjects might also be associated with the high carriage rate of the virus in their parents. Thus, in addition to the inherent host parasite interrelationship, the environmental factor might have also been responsible for this high occurrence of HBAg in these children.

The low incidence of HBAg in our undernourished subjects (Table 1) with poor socioeconomic status and impaired cellular immunity (Table 5), living in utmost poverty, hot climate and in poor hygienic environment, signalized the fact that neither of these factors was invariably associated with increased frequency of HBAg. On the contrary, it may be pointed out that our leprosy patients showing high incidence of HBAg were subject to all the above factors. Thus, it appears that a multifactorial host response (decreased CMI being one of multiple factors) might explain the HBAg carrier state. Moreover, the possibility that the persistence of HBAg might be genetically related must be considered (5). These authors found definite family clustering of the antigen among certain tropical and subtropical communities with high carriage rate of HBAg. Yap *et al* (32) also demonstrated the differential ethnic susceptibility among the Chinese, Malays and Indians in

Singapore. We also showed that there was some clustering of HBAg among the first degree relatives of the index cases with HBAg (Fig. 1). On several occasions, in our leprosaria, leprosy patients marry among themselves, so that there is more chance of having progeny with the homozygous state (Au'/Au'), an autosomal recessive gene that confers on the hosts an ability to maintain the antigen after acquiring it. Presently, we do not know the source of infection of HBAg in these children, but it is interesting that the subtypes of HBAg in the patients with leprosy and their children are comparable but not identical (Table 2). A detailed epidemiologic as well as family study among lepromatous families is likely to throw light on the possible genetic basis and immunologic mechanism for the persistent viremia in these individuals.

Subtype of HBAg in leprosy. The worldwide distribution of the subtypes of HBAg is not uniform ([3, 8, 12, 15, 19, 22]). However, the subtype relation of the persistent HBAg in leprosy patients has not yet been explored. In the present study, ay was the predominant subtype among leprosy patients (73%) as well as their apparently healthy children (78.6%). Furthermore, the two patients who developed icteric hepatitis also had ay subtype. Thus, from the epidemiologic points, while the previous study ([9]) had shown the preponderance of ay subtype among the voluntary blood donors in Delhi, and also in the patients with virus B hepatitis as well as hepatic cirrhosis; our present study conclusively proves ay to be the predominant subtype among leprosy patients and their offspring. This conforms with the recent studies of Pal *et al* ([21]) and Sama *et al* ([26]) who also observed ay to be the dominant subtype in India. Two leprosy patients and 11 children were asymptomatic carriers of HBAg belonging to only one subtype for at least four and two years, respectively. In only one child in our study was the r subtype detected. This is consistent with the study of Bancroft ([2]) who observed this subtype to be confined in the Far East only.

Persons developing HBAg positive hepatitis usually clear the antigen from their blood within six to twelve weeks of the onset of the disease ([7, 13]). In contrast, in two lepromatous patients of the present series, although clinical jaundice disappeared and the levels of serum bilirubin and enzymes declined considerably, HBAg was persistently present even 15 weeks after the period of maximum clinical illness (Table 3). This delayed elimination of HBAg without subsequent formation of its specific antibody in these two leprosy patients is similar to prolonged viremia in patients with unresolved viral hepatitis suppressed with prednisolone, and it may indicate an immunologic deficiency state characterized by ([31]) an inability to produce high avidity HBAb ([32]).

SUMMARY

Twenty-six hepatitis B antigen positive sera, obtained by screening samples from 135 biopsy proven lepromatous leprosy patients and 156 apparently healthy children of leprosy affected patients, were analyzed for surface antigens of Australia antigens. These sera represented 13 patients with lepromatous leprosy and 13 children of leprosy affected subjects. In the control group of healthy soldiers and severely undernourished subjects, only 22 of 68 hepatitis B positive sera obtained by screening 2,982 soldiers, and only one positive serum obtained by screening 34 undernourished individuals were also analyzed for surface antigens. All subjects in the various study groups, including both control groups, were institutionalized. Additionally, three HBAg positive sera from two lepromatous leprosy patients and one child of a leprosy patient were also included for subtyping. Thus a total of 52 hepatitis B antigen positive sera were tested for the a, d, y and r antigenic subdeterminants using absorbed human antibody in immunodiffusion test. Skin tests against five antigens were possible in some subjects in the four groups. All groups, except the soldiers, had shown some impairment of cellular immunity against various antigens. The carrier rate of HBAg was 9.6% in the children, although they had no clinical leprosy, and 10.3% in the patients with lepromatous leprosy who had an immunologic deficit. Of the control group, the incidence of HBAg among 2,982 soldiers living in a clean hygienic environment, presumably with high nutrition and immunity status, was 2.3%; and paradoxically, that in the severely undernourished subjects of low socio-economic status and with profound impairment of cellular immunity was 2.9%. Except for three patients with lepromatous leprosy who developed icteric hepatitis, all other individuals carried

HBAg in their blood for several years and did not show any clinical or biochemical manifestations of liver disease. Ay was the predominant subtype among all of these three groups. Ar was detected only in one child, while one HBAg positive serum could not be typed. In addition, the subtype remained unchanged in carriers for many years.

The high prevalence and persistence of HBAg among the offspring of leprosy patients in their very early life, especially when they were not suffering from any clinical leprosy, has been reported for the first time. Some clustering of the hepatitis associated virus in the members of families of the lepromatous patients has been observed.

From the data it appears that multiple factors such as environmental conditions, immune status, as well as genetic predisposition are all associated with the high carriage rate of HBAg.

RESUMEN

Con el fin de tipificar los antígenos de superficie, se estudiaron 26 sueros positivos para antígenos de la hepatitis B (antígeno Australia). Los sueros se obtuvieron a partir de 135 pacientes con lepra lepromatosa y de 156 niños descendientes de pacientes afectados y sin evidencias clínicas de la enfermedad. Trece de los sueros correspondieron a los pacientes y 13 a los niños. Los grupos control estuvieron formados por 2,982 soldados sanos y por 34 individuos severamente desnutridos. Se buscaron antígenos de superficie en 22 de 68 sueros positivos para hepatitis B correspondientes al grupo de los soldados y en el único suero positivo del grupo de los desnutridos. Incluyendo a otros dos sueros obtenidos de pacientes con lepra lepromatosa y al de otro niño familiar de un paciente con lepra, se tipificaron los determinantes antigénicos a, d y r, en un total de 52 sueros positivos para antígenos de la hepatitis B. En algunos individuos de los cuatro grupos fue posible realizar pruebas intradérmicas con 5 antígenos. Todos los grupos, excepto los soldados, mostraron cierta depresión en su inmunidad celular hacia varios antígenos. La proporción de portadores de HBAg fue del 9.6% en el grupo de los niños y del 10.3% en el grupo de los pacientes con lepra lepromatosa quienes mostraron deficiencias inmunológicas. La incidencia de HBAg entre los 2,982 soldados, habitantes de un medio ambiente higiénico y, presumiblemente, con un adecuado estado nutricional y apropiada inmunidad, fue del 2.3%. Paradójicamente, en el grupo de desnutridos severos, de baja condición socioeconómica y con alteraciones en su inmunidad celular, la incidencia fue del 2.9%. Excepto por 3 pacientes con lepra lepromatosa que desarrollaron hepatitis ictérica, todos los otros individuos tuvieron HBAg en su sangre durante varios años sin mostrar ninguna manifestación clínica o bioquímica de enfermedad hepática. Ay fue el subtipo predominante entre los grupos estudiados. Ar se encontró sólo en un niño y uno de los sueros positivos para HBAg no se pudo tipificar. Además, el subtipo permaneció sin cambiar durante muchos años.

Por primera vez se comunica la elevada incidencia y la persistencia de HBAg en la progenie de los pacientes con lepra en una etapa muy temprana de su vida y aún cuando ninguno de los niños presentó manifestaciones clínicas de la enfermedad. Dentro de las familias de los pacientes lepromatosos se observó cierto predominio de algunos subtipos de los virus asociados con hepatitis. De los datos presentados se concluye que múltiples factores tales como condiciones ambientales, estado inmune, así como cierta predisposición genética, están asociados con la elevada proporción de portadores de HBAg.

RÉSUMÉ

On a passé en revue des échantillons de sérum obtenus chez 135 malades souffrant de lèpre lépromateuse confirmée par l'examen histopathologique. On a également passé en revue des échantillons de sérum recueillis chez 156 enfants apparemment sains nés de parents atteints de lèpre. Parmi ces sérums, 26 ont été trouvés positifs pour l'antigène de l'hépatite B. Ces 26 échantillons ont été alors analysés afin de mettre en évidence les antigènes de surface des antigènes australiens. Ces échantillons de sérum provenaient de 13 malades atteints de lèpre lépromateuse, et de 13 enfants nés de parents atteints de lèpre. En ce qui concerne le groupe-témoin, 68 échantillons seulement ont été trouvés positifs pour l'hépatite B parmi les échantillons de sérum obtenus chez 2982 militaires en bonne santé. Dans un autre groupe témoin constitué par 34 individus en état de malnutrition grave, un seul a été trouvé positif. Ces échantillons obtenus chez des témoins ont été également analysés en vue d'étudier les antigènes de surface. Tous les sujets inclus dans ces différents groupes, y compris les 2 groupes témoins, étaient hospitalisés. De plus, on a également inclus dans l'étude 3 échantillons de sérum positifs pour HBAg obtenus chez 2 malades lépromateux et chez un enfant avec un parent lépreux. Ces 3 sérums ont été également inclus pour le typage en sousgroupes. En résumé, un total de 52 échantillons de sérum positifs pour l'antigène de l'hépatite B ont été étudiés en vue de mettre en évidence les déterminants antigéniques a, d, y et r. Pour ce faire, on a utilisé une méthode d'immunodiffusion utilisant des anticorps humains absorbés. Chez

quelques-uns des sujets appartenant à ces 4 groupes, il a été possible de procéder à des épreuves cutanées concernant ces 5 antigènes. Tous les groupes, à l'exception des militaires, ont montré une certaine détérioration de l'immunité cellulaire à l'égard des différents antigènes. Le taux de porteurs de HBAg était de 9,6% chez les enfants, quoique ceux-ci ne présentassent pas de lèpre clinique. Le taux de porteurs était de 10,3% chez les malades souffrant de lèpre lépromateuse qui présentaient un déficit immunologique. Dans le groupe-témoin, l'incidence de la HBAg chez 2982 militaires vivant dans un milieu hygiénique favorable, vraisemblablement bien nourris et présentant un état immunitaire satisfaisant, était de 2,3%. De manière paradoxale, le taux de porteurs chez les sujets en état de malnutrition grave et avec niveau socio-économique bas, souffrant par ailleurs de détérioration grave de l'immunité cellulaire, n'était que de 2,9%. A l'exception des 3 malades atteints de lèpre lépromateuse qui ont développé une hépatite ictérique, tous les autres individus porteurs de HBAg dans le sang pour plusieurs années, ne présentaient aucune manifestation clinique ou biochimique d'une atteinte hépatique. Ay était le sous-type prédominant dans, ces 3 groupes. Ar n'a été détecté que chez un enfant, alors qu' un sérum positif pour HBAg n'a pas pu être typé. De plus, le sous-type est resté inchangé chez les porteurs durant plusieurs années.

La prévalence élevée et la persistance de HBAg chez les enfants de parents atteints de lèpre au cours des stades très précoces de la vie, et spécialement lorsqu'ils ne présentaient aucune manifestation de lèpre clinique, est relaté ici pour la première fois. Une certaine aggrégation de HAV (virus associé a l'hépatite) a été observée chez les membres de la famille de malades lépromateux.

Cette donnée semble indiquer que de multiples facteurs, tels que les conditions de milieu, le statut immunitaire tout autant qu'une prédisposition génétique sont associés avec un taux de portage élevé de HBAg.

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