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Histocompatibility Antigens in Patients with Leprosy from Azarbaijan, Iran[1]

N. Mohagheghpour, H. Tabatabai, K. Mohammad, K. Ramanujam, and F. Z. Modabber[2]

Evidence in man indicates that the clinical picture in leprosy as well as the prognosis for patients with this disease parallels the efficacy of the host's cellular immune response ([6]). In lepromatous leprosy there is a marked deficiency of the cell-mediated immune response (CMI); such impairment is not a general feature of the tuberculoid form. The documented deficiency of CMI in patients with lepromatous leprosy has been suggested to be a consequence of intensive exposure to *Mycobacterium leprae* ([7]); however, the possibility that such a deficiency antedates infection cannot be overlooked. The familial pattern of leprosy as well as the high incidence in certain genetically-related populations have implicated a genetic predisposition for susceptibility to this disease ([1]).

Recent evidence concerning the association between susceptibility to certain diseases, major histocompatibility antigens, and immune responses ([9, 11, 13, 15]) warrants a search for the possible association of HLA antigens with manifestation of leprosy. Thus, in this study the HLA profiles of 88 Iranian patients with leprosy were compared with those of normal individuals from corresponding ethnic groups.

MATERIALS AND METHODS

Patients. Eighty-eight leprosy patients included in this investigation were from Baba Baghi Leprosarium in Western Azarbaijan, Iran. Patients were characterized by clinical, bacteriological, and histological examination. Sixty-five patients had the lepromatous form of leprosy (LL), 9 cases were borderline (BB), 7 were borderline with lepromatous features (BL), and 7 were indeterminate (I), using the Ridley and Jopling system ([19]).

All patients were from Eastern Azarbaijan. Fifty-nine patients were linguistically Turkish (Azeri Turkie) and 29 were Kurdish. Controls were 125 normal individuals from the same regions as the patients, including 101 Turks and 24 Kurds.

Serological methods. HLA antigens were identified by the standard microlymphocytotoxicity test ([22]), using typing trays obtained from Terasaki. Upon receipt, reactivity of the reagents was checked using HLA sera. Because of serological uncertainties, antigens A_9, A_{10}, AW_{19} and BW_{16} were not subdivided.

Data analysis. Statistical tests were performed using the Mantel-Haenszel procedure ([12]) to provide a one degree of freedom χ^2 for the differences in antigen frequency between patients and controls across the different ethnic groups. Adjustment to the nominal significance levels was made to account for the number of different comparisons being made. The ordinary chi square test was used for other comparisons. Relative risk (x) was calculated for significant associations according to the method described by Woolf ([25]).

RESULTS

In the two ethnic groups, Kurds and Turks, comparison of the frequencies of HLA antigens using the Mantel and Haenszel method did not reveal any differences between the patients with lepromatous leprosy or the total patient populations and the controls (The Table).

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[2] N. Mohagheghpour, Ph.D., Associate Professor, Department of Pathobiology, School of Public Health, H. Tabatabai, M.Sc., Research Assistant, Department of Pathobiology, School of Public Health, Teheran University, Teheran, Iran; K. Mohammad, Ph.D., Assistant Professor, Department of Epidemiology and Biostatistics, Teheran University; K. Ramanujam, M.D., Professor, Schieffelin Leprosy Research and Training Centre, Karagiri, North Arcot, Tamil Nadu, South India; F. Z. Modabber, Ph.D., Associate Professor, Department of Pathobiology and Institute of Biophysics and Biochemistry, Teheran University.

TABLE. *Comparison of HLA antigen frequencies (%) among leprosy patients and healthy controls.*

Antigen	Kurds			Turks		
	All patients (29)[b]	LL[a] patients (20)	Controls (24)	All patients (59)	LL patients (45)	Controls (101)
A_1	10	5	29	15	16	17
A_2	21	20	16	25	20	26
A_3	24	30	25	20	24	20
A_9	38	40	38	20	20	26
A_{10}	14	10	29	10	11	7
A_{11}	21	20	4	31	31	22
A_{28}	0	0	8	7	9	12
AW_{19}	31	35	25	34	38	29
B_5	28	25	38	39	38	34
B_7	3	0	4	5	4	7
B_8	10	15	4	10	11	6
B_{12}	21	15	17	12	13	14
B_{13}	3	5	0	10	7	6
B_{14}	3	5	4	3	4	4
B_{18}	14	15	13	8	11	7
B_{27}	3	5	0	2	2	5
BW_{15}	7	10	21	2	2	10
BW_{16}	14	15	33	12	16	5
BW_{17}	7	5	0	5	6	4
BW_{21}	7	5	8	2	2	8
BW_{22}	17	15	8	14	11	10
BW_{35}	31	40	8	36	36	35
BW_{37}	3	5	4	0	2	1
BW_{40}	3	0	8	12	13	8

[a] LL, lepromatous leprosy.
[b] Number of individuals tested.

Looking at the different groups individually, Kurdish speaking patients with the lepromatous form of the disease (LL patients) showed an increase in HLA-BW_{35} frequency (40%) as compared to the normal individuals (8%) ($p < 0.02$, $x = 7.3$) (The Table). The frequency of this antigen in the total patient population was also higher than that observed among the healthy Kurds ($p < 0.05$, $x = 5.0$). Moreover, HLA-A_1 showed a diminished frequency among the LL patients as compared to the controls ($p < 0.05$, $x = 0.13$). None of these comparisons, however, reached statistical significance when p values were corrected for the number of specificities (twenty-four) tested.

Comparison of the distribution of HLA antigens among the Turks revealed notable deviation in the percentage of HLA-BW_{15}, with 1/59 in patients and 10/101 (10%) in the controls ($p < 0.05$, $x = 0.16$). However, when corrected for the number of antigens tested, again, this difference was not statistically significant.

DISCUSSION

In view of the complexity of the genetic composition of the present day population in Iran, the HLA profiles of 88 leprosy patients from Azarbaijan Province were compared to those of 125 healthy, ethnically matched individuals. Among the Kurds, frequencies of HLA-A_1 and HLA-BW_{35} in patients with lepromatous leprosy were found to be different, with statistical significance at the 5% and 2% levels respectively from the percentage of these antigens in the healthy controls, without correction for the number of antigens tested. Differences in the distribution of HLA-BW_{35} remained significant when the total patient population was compared with the control group (uncorrected $p < 0.05$). The only association observed in the Turkish population was between leprosy and HLA-BW_{15} (uncorrected

$p < 0.05$). Comparison of the distribution of HLA antigens across the two ethnic groups, on the other hand, revealed only equivocal differences between the LL patients and the controls. Similarly frequencies of HLA antigens did not show a significant difference when the total patient population was compared with healthy individuals.

An earlier report from Iran has revealed a higher, but statistically insignificant, percentage of HLA-A_{11} antigen in patients with leprosy ([14]). Among the patients examined in the present investigation, the frequency of this antigen was only marginally elevated. It should be noted though that the population tested by Massoud, *et al.* ([14]) is not from a distinct ethnic group.

Including the present report, 13 groups have studied the distribution of HLA antigens among patients with leprosy ([3, 5, 8, 10, 14, 16, 17, 18, 20, 21, 23, 24]); significant associations were shown in six studies ([5, 8, 10, 16, 23, 24]). Such significant findings are strongly suggestive of a possible association between HLA antigens and susceptibility to leprosy, especially with a particular form of the disease, and cannot be regarded as a chance event. Moreover, family studies by de Vries, *et al.* ([4]) have clearly indicated that both susceptibility to and type of leprosy are controlled by at least two HLA-linked genes. In addition, twin studies provide strong evidence for some type of genetic influence in the predisposition towards leprosy ([2]). In view of these findings, studies of additional cases and controls and particularly haplotype frequencies seems to be justified.

SUMMARY

The distribution of 24 histocompatibility antigens in 88 Azerbaijani patients with leprosy was determined and compared with those of 125 normal, ethnically matched individuals. HLA-BW_{35} was increased in frequency among the Kurdish patients as compared to the controls; HLA-A_1, however, displayed decreased frequency in patients with the lepromatous form of the disease. Among the Turks, diminished frequency of HLA-BW_{15} was noted in the total patient population. None of these comparisons, however, reached statistical significance when corrected for the number of antigens tested. Across the two ethnic groups, differences in the frequencies of HLA antigens between the patients and the controls were only marginal.

RESUMEN

Se estudió la distribución de 24 antígenos de histocompatibilidad en 88 personas Azerbaijani con lepra y en 125 individuos sanos correspondientes al mismo grupo étnico. Comparando los resultados con aquellos encontrados en los controles, se observó que el antígeno HLA-BW_{35} tuvo una frecuencia más elevada en los pacientes Kurdos mientras que el HLA-A_1 tuvo una frecuencia disminuída en los pacientes con la forma lepromatosa de la enfermedad. Entre los Turcos, se observó una frecuencia disminuída del HLA-BW_{15} en la población total de enfermos. Ninguna de estas comparaciones, sin embargo, alcanzó significación estadística después de haber corregido los datos por el número de antígenos estudiados. Las diferencias en las frecuencias de los antígenos HLA en los pacientes y sus controles entre los dos grupos étnicos (Kurdos y Turcos) fueron tan sólo marginales.

RÉSUMÉ

La distribution de 24 antigènes d'histocamptabilité a été déterminée chez 88 malades de l'Azerbaïjan et comparée avec celle de 125 individus normaux, assortis sur le plan ethnique. L'antigène HLA-BW_{35} présentait une fréquence augmentée chez les malades kurdes, comparée aux témoins. Néamoins, la fréquence de HLA-A_1 était diminuée chez les malades atteints de la forme tuberculoïde. Chez les Turcs, dans l'ensemble des malades, on a observé une diminution de HLA-BW_{15}. Aucune de ces comparaisons, toutefois, n'a atteint un seuil de signification statistique, lorsque l'on prenait en compte le nombre d'antigènes étudiés. Les différences notées dans les fréquences d'antigènes HLA chez les malades et chez les témoins, dans les deux groupes ethniques, n'étaient que limites.

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