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ON THE ASSOCIATION BETWEEN HLA-A1 AND B5 AND CLINICAL FORMS OF SCHISTOSOMIASIS MANSONI

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The association between both HLA-A1 and B5 antigens and chronic forms of human schistosomiasis was studied in 64 patients and 26 normal controls from a southern Brazilian hospital. No apparent correlation between the chronic forms of the disease and the expression of those antigens was detected. However, the analysis of these data together with those observed on an Egyptian sample suggests that the presence of either of the antigens and the hepatomegalic forms of schistosomiasis is significant, without heterogeneity. Conversely, the association of histocompatibility antigens with splenomegaly is consistent and significant only for HLA-B5, but not HLA-A1.

Key words: schistosomiasis – susceptibility to infection – HLA system and disease

The infection of the human host by *Schistosoma mansoni* is characterized in most cases by mild forms of the disease or forms with no clinical manifestation whereas in a few individuals severe forms of the disease develop (Memoranda, WHO, 1974; Mahmoud, 1981). Apart from environmental causes for this variability, such as duration and intensity of exposure (Warren, 1973), the different forms of the disease seem to be correlated to the variable susceptibility of the host to the parasite which could depend on the host's genetic background.

Based on several reports on association between HLA antigens and disease (Dausset & Svejgaard, 1977), studies have been carried out to uncover possible associations between the clinical forms of schistosomiasis and the highly polymorphic HLA system. The observations by Abdel Salam et al. (1979) who suggested a high incidence of HLA-A1 and B5 alleles among individual affected by the hepatomegalic and splenomegalic forms of the disease, require further confirmation with different populations for an understanding of the role played by genetic mechanisms on the variability of clinical manifestation in chronic forms of schistosomiasis. The aim of the present paper was to investigate whether the results observed in Egypt could also be reproduced in a sample from a Brazilian population.

MATERIALS AND METHODS

Patients – The sample consisted of 64 patients from the *Hospital das Clínicas de São Paulo*, infected by *S. mansoni*, as demonstrated by stool examination, and 26 individuals from the same hospital with clinical symptoms other than those typical of schistosomiasis (including negative parasitological test), taken as controls. The São Paulo urban area is not endemic for schistosomiasis mansoni; therefore the controls were selected among patients from the north-eastern part of the country, as were the patients infected with *S. mansoni*. The 64 individuals with schistosomiasis were classified in three subgroups: a) those who had splenomegaly or hepato-splenomegaly and were considered as carriers of the severe form of the disease, b) those showing only hepatomegaly (moderate clinical form), and c) asymptomatic, i. e., those with intestinal infection but no other clinical signs or symptoms of the disease.

Antisera and microcitotoxicity test – A kit with 38 antisera for HLA was kindly provided by Prof. Victor Nussenzweig (NYU-USA), 16 for the HLA-A locus and 22 for the HLA-B locus. All patients and controls were tested for all 38 antigens by the usual microcitotoxicity techniques (Van Rood et al., 1975). As our main objective was centered on the A1 and B5

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antigens, the frequencies of these antigens were also compared with their frequences in other samples of the Brazilian population (Ferreira, E., personal communication).

Statistical analysis – The statistical methodology utilized was the conventional technique of analysis through 2 x 2 contingency tables, either with Yates' correction for continuity or using Woolf's (1955) method. In the last case, the correction for small samples was made according to Haldane (1956).

RESULTS

To test whether the frequencies of the A1 and B5 antigens in our sample differed from those in the southern Brazilian population, a comparison was made with the frequencies of both antigens obtained by Ferreira (Ferreira,

TABLE I

Distribution of HLA antigens A1 and B5 in 90 patients, with or without schistosomiasis mansoni, from a hospital in southern Brazil

Clinical form	A1		B5		A1 or B5	
	Present	Absent	Present	Absent	Present	Absent
Severe	4	15	4	15	8	11
Moderate	2	2	1	3	2	2
Asymptomatic	5	36	4	37	9	32
Control	3	23	7	19	9	17

TABLE II

Comparison of the distribution of HLA – A1 and B5 antigens in 90 patients of a hospital sample from southern Brazil

Subsample comparisons	A1 – Presence		B5 – Presence		A1 or B5 Presence	
	χ^2	Risk	χ^2	Risk	χ^2	Risk
Infected x Control	0.122	1.59	1.305	0.44	0.043	0.80
Severe x (MOD + ASY + CONT)[a]	0.151	1.63	0.007	1.31	0.786	1.85
Severe x (MOD + ASY)	0.029	1.45	0.699	2.13	1.240	2.25
(SEV + MOD) x Asymptomatic	1.141	2.54	0.900	2.56	2.321	2.73
Severe x Asymptomatic	0.255	1.92	0.623	2.47	1.699	2.58
Moderate x (ASY + CONT)	1.921	7.38	0.058	1.70	0.182	2.72
Moderate x Asymptomatic	1.609	7.20	0.009	3.08	0.405	3.56
Asymptomatic x Control	0.094	1.06	2.280	0.29	0.734	0.53

a: MOD = Moderate form; ASY = asymptomatic form; CONT = control; SEV = severe form.

TABLE III

Association between HLA – A1 and B5 antigens with hepatomegaly (Woof's method)

Samples	A1 – Antigen		B5 – Antigen	
	Relative Risk	χ^2	Relative Risk	χ^2
Southern Brazil (present study)	2.46	2.08	2.48	1.85
Northeastern Brazil (Pereira, 1979)	2.12	1.81	2.48	1.78
Egypt (Abdel Salam et al., 1979)	19.80	13.12	15.15	14.15
Significance (d.f. = 1)		11.46		13.39
Heterogeneity (d.f. = 2)		5.55		4.38

TABLE IV

Association between HLA – A1 and B5 antigens with splenomegaly (Woof's method)

Samples	A1 – Antigen		B5 – Antigen	
	Relative Risk	χ^2	Relative Risk	χ^2
Southern Brazil (present study)	1.49	0.39	2.14	1.27
Northeastern Brazil (Pereira, 1979)	2.37	2.39	1.48	0.51
Egypt (Abdel Salam et al., 1979)	28.02	18.13	10.76	11.66
Significance (d.f. = 1)		11.60		8.17
Heterogeneity (d.f. = 2)		9.31		5.27

E., personal communication). No statistical differences were detected ($\chi^2 = 0.50$ and 0.34, respectively for A1 and B5).

Tables I and II show the distribution of the A1 and B5 antigens in the subdivided sample and several comparisons made between subsamples. No significant differences were found. The same was obtained for the other 36 antigens studied (data not shown). For the A1 and B5 antigens, however, the sign test applied to the 16 comparisons shows that the presence of the A1 and B5 antigens increases the severity of the disease ($p < 0.01$). When the test is applied separately for A1 and B5, only A1 shows the same pattern ($p < 0.01$ and $p < 0.10$, respectively).

The joint analysis of these data and those of Abdel Salam et al. (1979), as well as from another Brazilian sample (Pereira, 1979) shows that the samples are homogeneous concerning to association of HLA-A1 and B5 and hepatomegaly, which is significant at the one percent level (Table III).

Table IV shows the associations between A1 and B5 antigens with splenomegaly. A significant heterogeneity was detected for A1-splenomegaly association. In this case, the observed significance cannot be accepted, since it may represent types I or II of statistical errors in either of the directions or it may simply mean that the susceptibility of individuals bearing the A1 antigen is not the same in different geographical areas.

DISCUSSION

The present results show that no estatistical differences are found when the clinical forms of human schistosomiasis from a non-endemic area in southern Brazil and normal controls are compared for the frequency of 38 HLA antigens of the A and B loci. However, further studies were carried out concerning antigens HLA-A1 and B5 since previous reports suggested that the frequencies of these antigens are higher in individuals showing the severe forms of the disease. The relative risk represented by the presence of A1 and B5 antigens was then calculated in our sample for all comparisons made. It should be pointed out that some of the comparisons are not independent. Nevertheless, the positive correlations observed in almost all comparisons suggests a clear association of these antigens with increased risk of any of the pathological signs which are characteristic of the disease. This is in accordance with the results reported by Abdel Salam et al. (1979) based on 51 Egyptian children infected by *S. mansoni*. Furthermore, the same test applied separately for A1 and B5 antigen, failed to reproduce the above results for the B5 antigen.

In contrast with our finding, Abdel Salam et al. (1979) observed that the association between both A1 and B5 antigens and liver enlargement was statistically significant. However, when both data are taken together, it was possible to show that they are hemogeneous and that a significant association is confirmed (Table III). The same was not true when spleen enlargement was concerned, since the samples are now clearly heterogeneous (Table IV), despite the disclosed statistical significance. The parasite's variability, a more complex cause for this association, like a linkage disequilibrium between a "susceptibility gene" and HLA (with differents alleles of the MHC complex system in disequilibrium in

differents populations), or even some pertinent environmental differences which the HLA effect is dependent on, may account for some of these apparent discrepancies.

Racial differences associated with severity of schistosomiasis are know to exist, Negroes showing a higher degree of resistance (Bina et al., 1978). Moreover, the A1 and B5 frequencies are higher in Whites than in Negroes (Arce Gomes, 1979). This racial effect could explain the apparent small excess of A1 and B5 in the present sample, but it is insuficient to account for the striking association observed in Egypt.

It is not possible to compare the risk of infection in Egypt and Brazil, since differences in cultural behaviour and in the prevalent endemic conditions probably exist. Assuming that the probability of people in endemic areas to become infected is the same in both countries, the risk of developing severe forms of schistosomiasis is certanly greater in Egypt than Brazil. On the other hand, the possibility that a similar study employing a larger Brazilian sample could disclose a comparable infection risk cannot be ruled out.

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