HLA and sexually transmitted diseases in prostitutes

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SUMMARY The HLA profile of 148 unrelated, Chinese prostitutes (56 with repeated gonococcal infection, 31 with syphilis, 31 with gonorrhoea and syphilis, and 30 with no evidence of infection) was compared with that of 238 unrelated, healthy, Chinese control subjects. The joint occurrence of AW19 B17 was observed in 25·8% of prostitutes with double infections compared with 6·7% of control subjects, while that of A11 B15, on the other hand, was associated with a resistance to syphilis and gonorrhoea. The latter profile was observed in 46·7% of prostitutes in business for more than two years who were resistant to disease, in 30% of prostitutes with an overall disease resistance, in 13·4% of control subjects, and in only 3·2% of prostitutes with combined syphilis and gonorrhoea. Because of the statistical uncertainty when multiple variables are being analysed these studies should be repeated in other groups of prostitutes of the same and different ethnic origins.

Introduction

Prostitutes are the major source of sexually transmitted diseases in Singapore (Khoo *et al.*, 1977). Some prostitutes have repeated infections while others are quite resistant to infection. While exposure to the causative organisms is an obvious explanation, another reason may be the differences in the immune response of the host to these organisms. The control of immune responses to synthetic antigens by immune response (IR) genes associated with the major histocompatibility locus has been clearly demonstrated in animals (Snell *et al.*, 1976). Recently, there has been evidence which suggests that IR genes associated with the major histocompatibility locus (HLA) may also exist in man (Blumenthal *et al.*, 1964; McMichael and McDevitt, 1977; Vries *et al.*, 1977). Thus, if the functions of immune response genes influence the susceptibility or resistance to venereal disease organisms in these prostitutes, these differences may be reflected in their HLA profiles. The results of HLA typing in prostitutes who are susceptible to and in those who are resistant to venereal diseases are reported in this paper.

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Material and methods

STUDY POPULATION

A total of 148 unrelated, Chinese, female prostitutes were HLA-typed and the HLA profile compared with that of 238 unrelated, healthy, Chinese, control subjects. The control group consisted of normal, healthy babies born consecutively at a maternity hospital in Singapore over a period of nine months. Both parents were of Chinese ethnic origin, the same ethnic group as the prostitutes. All the prostitutes, who carry medical cards which are regularly checked, are seen at the Middle Road Hospital every two weeks for periods ranging from one to 20 years. Cervical and rectal swabs for culture of gonococci are taken at every visit, and serological tests for syphilis (Venereal Disease Research Laboratory and fluorescent treponemal antibody absorption tests) are performed every three months.

The prostitutes were subdivided into four groups; the ages and the time of exposure to infection of each group is given in Table 1.

Group 1

This group consisted of 56 patients with repeated gonococcal infections diagnosed by positive culture results. The average number of infections was 5·4 per year per patient, ranging from two to 24 infections per year, and the average interval before the first infection was 3·4 months.

Table 1 Details of age and exposure to infection of 148 Chinese prostitutes

Patient group	Age (years)		Exposure to infection (years)*	
	Mean	Range	Mean	Range
1	35.8	18-53	5.5	1-17
2	39.3	23-55	10	1-20
3	37.3	24-56	6.7	1-20
4	32.5	19-52	4.3	1-20

* Estimated from the date each patient became a prostitute to the time of the study

Group 2

This group consisted of 31 patients with latent syphilis who had been treated and at the time of the study had no symptoms or signs of infection.

Group 3

This group consisted of 31 patients with combined infections. Serological tests for syphilis and repeated

cultures for gonococci both gave positive results. The average number of infections was 4.2 per year per patient, ranging from two to nine per year, and the average interval before the first infection was four months.

Group 4

This group consisted of 30 patients who had been exposed to gonorrhoea and syphilis for at least one year but were resistant to infection.

HLA TYPING

HLA typing was performed using the NIH (National Institutes of Health) lymphocyte micro-cytotoxicity method (National Institute of Allergy and Infectious Diseases, 1976-77). A total of 196 antisera defining 26 specificities were used. HLA typing sera were obtained from our own laboratory, the NIH serum bank, and direct from other laboratories. The sera defining A11, AW19, B15, and B17 are listed in Table 2.

Table 2 Antisera used to define A11, AW19, B15, and B17

Specificity	Antiserum		Contributor
HLA-A11	Ross	2-70-3-04-07-01	NIH
	Davies	2-70-3-11-29-01	NIH
	Tellier	2-71-4-07-12-01	NIH
	S97/27		Singapore
	S98/95		Singapore
	S84/19		Singapore
	S101/56		Singapore
	AH184		Singapore
'AW19 complex'	AH44		Singapore
AW30	Ortiz	2-50-5-08-13-01	NIH
	Abrams	2-73-2-02-10-01	NIH
	KC-OR	2-50-5-05-23-01	NIH
	Goggins	2-71-4-05-17-01	NIH
	Merle		Dausset
AW30 + AW31	S. Ouwenhand	1-46-5-02-12-01	NIH
AW30 + AW31	KR4282	1-46-5-02-12-01	NIH
AW30 + AW31	cc40	2-61-4-01-09-01	NIH
AW32 + AW25	Thompson	2-50-6-04-13-02	NIH
<AW33	Rabatin	2-65-1-07-23-01	NIH
AW30 + 31 + 32 + 33 + A10	Ortiz	2-50-8-05-11-02	NIH
AW30 + 31 + 32 + 33	cc23.1	2-61-1-06-24-01	NIH
AW30 + 31 + 32 + 33	cc23.2	2-61-1-08-12-01	NIH
AW30 + 31 + 33 + A10	Quinones	2-57-0-05-05-01	NIH
AW32 + weak reaction	Castenda	2-50-1-09-09-01	NIH
B15	TH-WGJ		Thorsby
B15 + BW35	Tuit 12371	1-04-1-02-07-01	NIH
	Templer	2-83-2-12-01-01	NIH
	Staats	1-04-5-04-24-01	NIH
	W. Eickel	1-04-3-06-13-01	NIH
	G. W. Klomp	1-15-0-07-02-01	NIH
	S18/05R1		Singapore
	305K		Betuel
	S87/58		Singapore
B15 + weak reaction	MMM	1-36-3-11-13-01	NIH
B15 + B17 + Sin 2 +	118E		Betuel
B15 + B17 + Sin 2 +	Sired		Joysey
B17	W. H. Wikkers	1-15-1-05-05-01	NIH
	P. Duwenhand	1-04-2-12-20-01	NIH
	cc61	2-61-4-10-30-01	NIH
	S. M. Abela		Hayes
	M. Daw		Hayes
	S102/16		Singapore
	S101/26		Singapore
	S18/26R1		Singapore

Results

The HLA antigen frequencies of the various groups of prostitutes and controls are shown in Table 3. The frequency of BW46 was significantly higher in the group with gonorrhoea and syphilis combined (group 3) whereas that of A2 was significantly lower in the resistant group (group 4) when compared with the controls. This difference, however, was not significant when corrected for the number of antigens typed.

Certain HLA-A-locus antigens occurred more frequently than expected with a specific B-locus antigen, a situation termed 'linkage disequilibrium'. The joint occurrences of AW19 B17 and A11 B15 in the various groups of prostitutes and in the controls are shown in Table 4. The joint occurrence of AW19 B17 was seen in eight (25.8%) out of 31 prostitutes with gonorrhoea and syphilis combined compared with 16 (6.7%) out of 238 controls ($\chi^2 = 12.29$; $P < 0.0005$; relative risk = 4.83). The joint

occurrence of A11 B15, on the other hand, was observed in nine (30%) out of 31 prostitutes resistant to disease compared with 32 (13.4%) out of 238 controls ($\chi^2 = 5.16$; $P < 0.025$) and one (3.2%) out of 31 prostitutes with combined infections ($\chi^2 = 5.84$; $P < 0.025$). Of the 30 prostitutes who were resistant to disease, 15 had been exposed for more than two years; of these 15, A11 B15 was observed in seven (46.7%) patients. The differences in the frequency of A11 B15 between this subgroup of prostitutes (exposed for more than two years and yet resistant to disease) and the controls ($\chi^2 = 11.9$; $P < 0.001$) and prostitutes with double infections ($P = 0.0008$) were even more pronounced.

Discussion

Caution must be exercised in interpreting the significance of a joint occurrence of antigens from two linked loci, since a large number of combinations (180 in this instance) are possible, and significant

Table 3 Frequencies of HLA in Chinese prostitutes and controls

HLA	Prostitutes				Total no. resistant (group 4, n = 30)	Controls (n = 238)
	With gonorrhoea (group 1, n = 56)	With syphilis (group 2, n = 31)	With gonorrhoea and syphilis (group 3, n = 31)	Total no. infected (n = 118)		
A1	0	6.5	0	1.7	0	0
2	62.5	58.1	61.3	61.0	30.0*	52.9
3	0	3.2	3.2	1.7	3.3	0.4
9	32.1	32.3	35.5	33.1	43.3	27.3
10	5.4	3.2	9.7	5.9	6.7	5.0
11	48.2	58.1	45.2	50.0	60.0	60.5
28	1.8	0	0	0.8	0	0.4
29	1.8	0	3.2	1.7	3.3	1.3
AW19	17.9	9.7	32.3	19.5	23.3	20.6
B5	10.7	9.7	9.7	10.2	13.3	12.6
7	1.8	0	3.2	1.7	3.3	1.7
8	0	0	0	0	0	0.4
12	1.8	3.2	0	1.7	6.7	3.4
13	16.1	16.1	16.1	16.2	23.3	20.2
14	0	0	0	0	0	0
15	32.1	29.0	22.6	28.8	33.3	22.3
17	17.9	12.9	25.8	18.6	13.3	14.3
18	0	0	0	0	0	1.7
27	3.6	6.5	5.1	5.1	0	7.1
37	1.8	0	0	0.8	0	0.4
40	36.4	35.5	32.3	34.7	38.7	40.0
BW16	16.1	16.1	16.1	16.1	9.7	10.0
21	0	0	0	0	0	0
22	5.4	9.7	16.1	9.3	10.0	12.2
35	10.7	6.5	0	6.8	0	4.6
46	28.6	25.8	38.7*	30.5	13.3	22.7

*In comparison of patient group with controls $P \leq 0.05$

Table 4 Joint occurrences of locus A and B antigens in various groups of prostitutes and in the controls

Antigen	Prostitutes									
	With gonorrhoea (n = 56)		With syphilis (n = 31)		With gonorrhoea and syphilis (n = 31)		Resistant (n = 30)		Controls (n = 238)	
	No.	%	No.	%	No.	%	No.	%	No.	%
AW19 B17	5	8.9	2	6.5	8	25.8*	2	6.7	16	6.7
A11 B15	10	17.9	4	12.9	1	3.2	9	30.0†	32	13.4

* Difference between patient group and controls, $\chi^2 = 12.97$; $P < 0.0005$; relative risk = 4.83

† Difference between patient group and controls, $\chi^2 = 5.64$; $P < 0.025$; cross product = 2.76

associations may be detected by chance. In fact, after correction for the number of combinations tested (P value $\times 180$) none of the P values are significant. Because the correct method of statistical analysis for this type of data, however, is by no means established, further studies are clearly necessary, since our study suggests that there may be HLA associations both in the susceptibility and in the resistance to venereal disease in prostitutes. The association appeared to be with the joint occurrence of A-locus and B-locus antigens. The frequency with which AW19 B17 occurred was significantly higher in prostitutes with both gonorrhoea and syphilis (25.8%) than in normal controls (6.7%) or other groups of prostitutes.

The joint occurrence of A11 B15 was more frequent among prostitutes who were resistant to disease (30%) than in controls (13.4%). The association of A11 B15 within the resistant group was even stronger when only those uninfected prostitutes who had been in business for over two years were included in the group (46.7%). On the other hand, the frequency with which A11 B15 occurred was very low among prostitutes with double infections (3.2%). It thus appears that A11 B15 was associated with a resistance to syphilis and gonorrhoea. Direct evidence of exposure to syphilitic and gonococcal organisms in this group of prostitutes would be difficult to obtain. This group of prostitutes operates in the same area as the other groups, and all the prostitutes in this group had been in business for more than a year, (15 (50%) out of 30 for more than two years and 10 (33%) out of 30 for more than five years). Singapore is also a major port and tourism is one of its main industries. It seems likely, therefore, that this group had been exposed to syphilis and gonorrhoea.

Confirmation of the joint occurrences of A-locus and B-locus antigens would suggest that the genes

which influence disease susceptibility and resistance are present in linkage disequilibrium with the major histocompatibility locus genes. These genes may be immune-response genes modifying the host's response to these sexually transmissible organisms, though other possibilities, such as genes which regulate the biochemical factors in vaginal secretions which prevent bacterial colonisation—for example, pH or lysozyme content—must be considered. If IR genes are concerned it may be possible to confirm this hypothesis by using assays of cellular immune response to gonococcal and treponemal antigens *in vitro*. Though these results may not have immediate clinical significance, it is possible that they could lead to new immunotherapeutic approaches to infectious diseases in general.

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