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INCREASED FREQUENCY OF HLA B17 ANTIGEN IN GIRLS WITH TURNER SYNDROME AND THEIR FATHERS

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SUMMARY

HLA-A, -B and -DR antigen distribution was studied in 49 girls with Turner Syndrome (TS), in 43 of their parents, as well as in 433 controls. No increased frequency of DR3, DR4 was found in our group. However, an increased frequency of HLA B17 antigen was disclosed (18.3% in TS versus 6.4% in the controls, $p<0.001$ and $p_{c<}0.01$). Furthermore, the HLA B17 antigen was of paternal origin in 77.7% of the cases. The interpretation of the present findings is quite difficult. Most likely, the findings are related to the chromosomal abnormality rather than to autoimmunity. It is quite possible that genes within the region of class I genes create unfavorable circumstances leading to the loss of the sex chromosome or, alternatively, genes in this region confer protection and prevent miscarriage of the affected fetus.

KEY WORDS: Turner Syndrome HLA antigens

INTRODUCTION

Glucose intolerance and autoimmune phenomena are more frequently encountered in girls with Turner Syndrome (TS) than in the general population (Cassidy *et al.*, 1978; Grunciro de Papendik *et al.*, 1987; Larizza *et al.*, 1989). A study was designed to investigate the diabetic tendency in girls with Turner Syndrome by determining, among other parameters, the HLA-A, -B and -DR antigens. An interesting, unexpected finding, of increased frequency of HLA B17 antigen emerged which is reported here-in.*

MATERIALS AND METHODS

HLA-A, -B and -DR antigen distribution was studied in 49 girls with Turner Syndrome and in 43 of their parents. 433 healthy, unrelated individuals served as controls. All subjects tested were of Greek origin. Almost 90% of the cases of TS were examined for shortness of stature. A few girls presented with lyphedema in the neonatal period and one presented with hypertension. Their chromosome constitution is depicted in Table 1 (A). The typing of HLA-A, -B and -DR antigens was

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Table 1: Chromosome Constitution of studied patients.

A. In the total group, tested	B. In girls wih TS and B17 antigen
45X:22 (45%)	45X: 6 (60%)
45X/46XX:8 (16.3%)	45X/46XX: 4 (40%)
46XiXq:7 (14.2%)	
Miscel: 12 (24.5%)	

performed by the classical two-step microlymphocytotoxicity test. The isolation of the cells was carried out by monoclonal antibodies specific for CD8 antigen (for HLA-A, -B typing) or DR β chain monomorphic epitope (for HLA-DR typing), using immunomagnetic isolation techniques. The control subjects were blood donors and hospital personnel. The results were analysed using the chi square test.

RESULTS

The HLA-A, -B antigens, which were tested, their % frequency in TS girls and controls, as well as the difference in antigen distribution (indicated by p value) are shown in Table 2. The frequency of HLA-DR3 and -DR4 antigen did not differ in girls with TS, in comparison to the controls.

The HLA-B17 antigen was found in 9 girls with TS (18,3%) and in 28 of the controls (6.4%). This difference was statistically significant ($p<0.001$, $p_c<0.01$). The frequency of the B17 antigen in the fathers tested was 16.3% ($p<0.01$), while in the mothers it was 4.5%.

Of the 9 girls, who possessed HLA B17 antigen, 7 inherited the antigen from their father, one from the mother, while in one B17 antigen was inherited from both parents. Thus, the HLA B17 antigen was of paternal origin in 77.7% of the girls. The distribution of the HLA-B17 antigen, according to chromosome constitution, is depicted in table 1 (B) and it shows that all girls with this antigen had, either, 45X or 45X/46XX mosaic.

DISCUSSION

No increased frequency of HLA-DR3 and -DR4 antigens was noticed in our group, another indication that the pathogenesis of glucose intolerance in girls with TS is different from that of type I diabetes mellitus. It is quite interesting, however, that the HLA-B17 antigen was more frequently observed in girls with TS (18.3% versus 6.4% in the controls). The number of subjects studied does not allow an evaluation of the effect of the type of chromosomal aberration (Table 1B). It may be pertinent, however, that 6 of the 10 cases were 45X and the remaining were 45X/46XX mosaic. Most interesting was the observation that in 77.7% of the cases the HLA B17 antigen was of paternal origin.

Table 2: Distribution (%) of HLA-A, -B antigens tested in subjects with Turner Syndrome and in controls.

	Controls (n=433)	TS girls (n=49)	
HLA	%	%	P
A-1	24	14.2	N.S.
2	53.1	50	N.S.
3	13.6	11.9	N.S.
9	33	30.9	N.S.
10	11.5	9.5	N.S.
11	10.6	9.5	N.S.
19	22.1	30.9	N.S.
28	5.7	14.2	N.S.
B-5	28.8	26.1	N.S.
7	8.1	4.7	N.S.
8	9.7	9.5	N.S.
12	17.5	14.2	N.S.
13	3.2	4.7	N.S.
14	5.3	2.3	N.S.
15	6.4	4.7	N.S.
16	8	7.1	N.S.
17	6.4	18.3	$p < 0.001$*
18	19.6	21	N.S.
21	8.1	12	N.S.
22	6.2	2.3	N.S.
27	5.7	4.7	N.S.
35	31.6	35.7	N.S.
37	3.4	0	N.S.
40	9	4.7	N.S.

* $p < 0.01$ after correction for the number of antigens tested.

Cassidy *et al.* (1978) in studying 23 girls with TS found no increased frequency in any of the HLA antigens tested. Their population group however was rather small. It should also be mentioned that in a study of 46 girls with TS from Northern Italy ((Larizza *et al.*, 1989) aiming at the evaluation of their autoimmune tendency, a high frequency of HLA-B38 and -A31 antigen was observed. However, the difference from the controls, in this sample, was not significant, after correction for the number of antigens tested. Thus far, the HLA-B17 antigen has not been associated with any autoimmune disorder and our findings should not be related to the autoimmune phenomena known to occur more frequently in TS. Hence, another relation of the finding, if any, to the syndrome should be sought. On the other hand it has been shown that the lost sex chromosome in TS is paternal in about 80% of the cases (Hassold *et al.*, 1991; Loughlin *et al.*, 1991; Cockwell *et al.*, 1991) and it may not be irrelevant that the HLA-B17 antigen, in our study of girls with TS, was paternal in 77.7% of the cases. Furthermore, southern blot analysis of human genomic DNA with HLA Class I cDNA probes (Trowsdale *et al.*, 1991) supports the idea that the HLA-class I gene family includes genes apart from those encoding HLA-A, -B and -C antigens.

Based on the above, admittedly limited, data, one would like to speculate that gene(s) within the HLA-class I region could create unfavorable circumstances leading to the loss of the sex chromosome. Alternatively, gene(s) in these loci perhaps offer protection and prevent miscarriage, which is known to be a very frequent event in XO embryos.

It is obvious that the precise interpretation and significance of the increased frequency of HLA-B17 antigen in girls with TS, inherited from their fathers, must await further studies.

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