HLA and Habitual Abortion

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The present study was undertaken to explore the degree of HLA compatibility in couples with repeated spontaneous abortions and the role of the class 2 antibody for the maintenance of pregnancy. For these purposes, HLA class 1 and class 2 antigen types were investigated in 8 couples with habitual abortions.

Table 1

<table>
<thead>
<tr>
<th>No. of Shared Antigens</th>
<th>HLA Couples n = 8</th>
<th>Control Couples n = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (12.5%)</td>
<td>2 (30%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (25%)</td>
<td>12 (18.5%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (37.5%)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (37.5%)</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>5</td>
<td>1 (12.5%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>6</td>
<td>1 (12.5%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2 (30%)</td>
</tr>
</tbody>
</table>

All of these couples shared the identical class 1 or 2 antigen types although the coincidence ratio obtained from the control 65 couples was 97 percent (statistically not significant). (Table 1) However, there was a tendency toward sharing at the HLA class 2 loci among aborting couples. The number of couples that shared identical class 2 antigens were 4/8 (50%) at the DR, 6/8 (75%) at the DR 52, 53 and 7/8 (87.5%) at the DQ loci in habitual aborters, and 83/221 (37.5%) at the DR, 125/221 (65.6%) at the DR 52, 53 and 133/221 (60.1%) at the DQ loci, respectively. Couples of habitual aborters had a high compatibility ratio of class 2 antigen compared with control couples. (Table 2)
Then, the result that half of these 8 couples shared antigens at the three loci of class 2 antigens was especially noteworthy. The ratio of shared antigens at the three loci was 18% in the control couples. (Table 3)

Table 3
Compatibility of HLA Class II (III Locus)
DR Locus, DR52,53 Locus and DQ Locus

<table>
<thead>
<tr>
<th>Locus</th>
<th>H.A. Couples</th>
<th>Control Couples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Locus</td>
<td>3/8 (37.5%)</td>
<td>33/221 (15%)</td>
</tr>
<tr>
<td>2 Locus</td>
<td>1/8 (12.5%)</td>
<td>57/221 (26%)</td>
</tr>
<tr>
<td>3 Locus</td>
<td>4/8 (50%)</td>
<td>40/221 (18%)</td>
</tr>
</tbody>
</table>

Those results suggested that the sharing of class 2 alleles between partners in a couple is possibly responsible for ideopathic fetal losses. These findings are compatible with either an immunologic or genetic mechanism. However, the association of a recessive lethal gene linked to the class 2 loci with the fetal wastage remains unknown, favoring the immunologic interpretation. Greater sharing at the class 2 loci is responsible for depression of immune responsiveness of maternal lymphocytes to paternal lymphocytes, being an important pathogenic mechanism in the embryonic and fetal losses. On this subject, the production of the class 2 antibody should play an important role for the maintenance of pregnancy. Thus, changes of antibody titer following the conception were investigated in two patients with habitual abortion. Titration of class 1 and class 2 antibody were performed by the use of the Antihuman Globulin microlymphocytotoxicity test and the B-warm assay, respectively. The types of HLA antigens sharing between the couple were A2, DRw52, and DQw3. The class 1 antibody which was specific for the Bw 60, was present continuously during the gestation. However, the presence of class 2 antibody was observed at the 13 weeks of gestation only. (Table 4, 5).
The class 1 antibody which was specific for the B51 and the Bw52 complexes, was decreased with the advance of gestation in case 2. Class 2 antibody was detected at the 19 and 24 gestational weeks, but it could not be detected at the 27 gestational weeks when the E.P.H. gestosis had concurred. (Table 6.7.)

**Table 4**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>M.Y. 28 y.o. G3PO</th>
</tr>
</thead>
</table>
| Past Pregnancies | 1) 23 y.o. 18G.W. Sp. Ab.  
2) 24 y.o. 21 G.W. Sp. Ab.  
3) 26 y.o. 11 G.W. Sp. Ab.  
4) 27 y.o. 10 G.W. Sp. Ab.  
5) 27 y.o. 0 G.W. Sp. Ab. |
| Menstrual History | Menarche 17 y.o.  
Cycle 28 days Regular |
| Past History | n.p. |
| Chromosomal Analysis | Patient and Husband Normal |
| Blood Type Analysis | Patient A, Rh D (+) CcDee  
Husband B, Rh D (+) CcDee  
Indirect Coombs' Test (-) |

**Table 5**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Relation between Titer of HLA Antibody and Gestation</th>
</tr>
</thead>
</table>
| Titer  | 32  
16  
8  
4  
0 |
| Gestational weeks | 11  
14  
17  
20  
23  
26  
29  
32  
35  |

**Table 6**

<table>
<thead>
<tr>
<th>Case 2</th>
<th>M.S. 29 y.o. G3PO</th>
</tr>
</thead>
</table>
| Past Pregnancies | 1) 25 y.o. 27 G.W. I.U.F.D.  
2) 26 y.o. 21 G.W. I.U.F.D.  
3) 27 y.o. 21 G.W. I.U.F.D. |
| Menstrual History | Menarche 17 y.o.  
Cycle 29 days Regular |
| Past History | 10 y.o. Appendectomy  
15 y.o. Atopic Dermatitis  
20 y.o. Duodenal Ulcer |
| Chromosomal Analysis | Patient and Husband Normal |
| Blood Type Analysis | Patient A, Rh D (+) CcDee  
Husband B, Rh D (+) CcDee  
Indirect Coombs' Test (-) |

**Table 7**

<table>
<thead>
<tr>
<th>Case 2</th>
<th>Relation between Titer of HLA Antibody and Gestation</th>
</tr>
</thead>
</table>
| Titer  | 16  
12  
8  
4  
0 |
| Gestational weeks | 11  
14  
17  
20  
23  
26  
29  
32  
35  |

- 27 -
The role of class 1 and class 2 antibody to maintain the pregnancy remained unknown in the present study, because antibody production of habitual aborters was variable during the pregnancy. Further accumulation of data concerning HLA class 2 antibody following the conception is absolutely necessary.