Tourette Disorder and HLA Typing

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HLA A, B, C and DR were typed in 73 Korean patients with Tourette disorder meeting the diagnostic criteria of DSM III-R and compared with 291 normal subjects. Relatively higher frequencies were found in HLA A11 and A26(10) with lower incidences in HLA A24(9) and B13. A family history of tic disorders was associated with a lower frequency of HLA A24(9).

Key Words: Tourette disorder, HLA

Tourette disorder is a complex neuropsychiatric disorder which is not as rare as originally believed. It has been found world-wide in all racial groups including Koreans (Min and Lee 1986). Its characteristic symptom manifestations including behavioral problems such as obsessive-compulsive disorder, genetic nature, an etiological anatomical localization in the brain and the effectiveness of drugs such as haloperidol, has stimulated vigorous research for a single etiology. However, the precise etiology is yet unknown. A neurotransmitter abnormality, particularly dopamine, has been suggested as one of major causes to date (Caine 1985). In genetics, recent studies indicate that an autosomal dominant gene with incomplete penetrance is the most likely mechanism (Pauls et al. 1990). In addition, many investigators agree that classical Tourette’s syndrome, chronic multiple motor or phonic tic and transient tic disorder likely represent variants of the same illness (Kurlan 1989) and that even obsessive-compulsive disorder as well as other related behavior disorders are probably an expression of the antici-

pated gene of Tourette’s syndrome (Comings 1987).

The HLA complex, a highly polymorphic gene cluster controlling cell surface antigen and serum complement factors, has been found to be associated with various disorders including psychiatric disorders (Tiwari and Terasaki 1985). The gene for HLA complex is found to be located in chromosome 6. The HLA system has been used in genetic studies as well as in testing histocompatibility and in immunological studies.

As Tourette disorder is recognized as highly genetic, attempts have been made to identify genetic association between HLA factors and the Tourette disorder. Though there is no evidence of immunologic etiology for Tourette syndrome, the relationship between Tourette syndrome and allergic response (Bruun 1984, Mandel 1986, Rapp 1986) also suggests a possible abnormality in the HLA system in patients with Tourette disorder.

Two studies have been reported to date on HLA typing in patients with Tourette disorder. Coming et al (1982) found, in a study of 12 patients with Tourette syndrome and their family members, that there was no predominant HLA-A or B associated with this disorder. Caine et al (1985) had found neither association between Tourette syndrome and HLA-A, B, C or DR nor evidence for a close linkage between a gene locus determining susceptibility to Tourette syndrome and the HLA loci. These two studies have limited conclusions as the number of subjects was small, and since these studies, many other new antigens have been found.
In Korea, clinical profile and familial tendency of Tourette syndrome are almost identical to those in other races (Min and Lee 1986; Lee and Min 1989). Koreans demonstrates that they share several distinctive characteristics with other Asians, though there are also significant differences when comparing Koreans with other Asians (Kim et al. 1986). The purpose of this investigation was to study the possible association between the HLA factors and Tourette disorder, with special regard to a family history of tic disorders.

SUBJECTS AND METHODS

Of the patients with Tourette disorder who registered in the Tourette Clinic of Yonsei University Medical Center, 73 unrelated patients were tested for HLA types. Males were 8 times more common than females. Age ranged from 4 to 24 years, with the most common being the 5 to 14 year group (60 patients). The diagnosis of Tourette disorder was made according to the criteria of DSM-III-R (American Psychiatric Association 1987) based on interviews using a semistructured schedule for this study by two psychiatrists (Drs. Min and Lee). None of the patients had ever taken drugs before coming to the clinic. They were evaluated with Achenbach's Child Behavior Check List (CBCL), intelligence test, handedness and EEG. History intake included a family history for Tourette's syndrome, chronic motor tic (CMT) and chronic vocal tic (CVT). The patient group was divided into two: a positive family history group and a negative family history group. Of the 73 patients, 31 belonged to the positive family history group and 29 belonged to the negative family history group. In the remaining 13 patients, family history could not be defined. All the subjects were verbally given informations about HLA typing and consent was obtained from the subjects or one of their parents.

For comparison, a total of 291 healthy living unrelated kidney donors provided the control material during the same period of study. They were Koreans of both sexes, and their age ranged from 25 to 49 years.

The HLA typing was performed on lymphocytes from peripheral blood of the subjects at the surgical immunology laboratory of Yonsei University Medical Center. A technique modified from the Terasaki method (Amos et al. 1980) was used. Antiserum was provided by Terasaki Laboratory (lot number 33, 34 and 35). A total of 79 HLA antigens were tested. HLA types were designated according to the 8lh Workshop Nomenclature (Terasaki, 1980).

The frequency of each antigen was compared between patients with Tourette disorder and the normal control group using the chi-square test. For correction of type II error, the P-values were multiplied by 69, the member of antigen tested. Of 79 antigens tested, 10 were not found in Koreans. Uncorrected P values were also presented. Statistical comparison was made between the patient group and the normal control group, between the positive or negative family history group and the control group, and between positive and negative family history groups.

<table>
<thead>
<tr>
<th>HLA antigens</th>
<th>Normal control N=291</th>
<th>Tourette disorder N=73</th>
<th>TD with family history N=31</th>
<th>TD without family history N=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>47(16.2)</td>
<td>20(27.4)*</td>
<td>8(25.8)</td>
<td>8(27.6)</td>
</tr>
<tr>
<td>A24(9)</td>
<td>125(43.0)</td>
<td>19(26.0)**</td>
<td>7(22.6)*</td>
<td>10(34.5)</td>
</tr>
<tr>
<td>A26(10)</td>
<td>31(10.7)</td>
<td>18(24.7)**</td>
<td>7(22.6)</td>
<td>6(20.7)</td>
</tr>
<tr>
<td>B13</td>
<td>27(9.3)</td>
<td>1(1.4)*</td>
<td>1(3.2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>B14</td>
<td>7(2.4)</td>
<td>3(4.1)</td>
<td>3(9.7)*</td>
<td>0(0)</td>
</tr>
<tr>
<td>B16</td>
<td>3(1.0)</td>
<td>3(4.1)</td>
<td>1(3.2)</td>
<td>2(6.9)*</td>
</tr>
<tr>
<td>Cw1</td>
<td>108(37.1)</td>
<td>19(29.0)</td>
<td>9(29.0)</td>
<td>5(17.2)*</td>
</tr>
<tr>
<td>DR4</td>
<td>98(33.7)</td>
<td>33(45.2)</td>
<td>13(41.9)</td>
<td>18(62.1)**</td>
</tr>
</tbody>
</table>

*, **, ***: Significantly different compared to normal control group in x²-test without correction at p<0.05, p<0.01, and p<0.005 respectively
RESULTS

Without correction of P values, several antigens were significantly different between the patient and control groups (Table 1). The antigens with higher frequencies in Tourette patients than the control group were HLA A11 and A26 (10) and those with lower frequencies were HLA A24 (9) and B13. The positive family history group had higher frequency than the control group in HLA B14 and lower frequency in HLA-A24 (9). The negative family history group had a higher frequency in DR4, and lower frequencies in Cw1. There were statistical differences in HLA B16, however, as their frequency were too small (less than 5) to be meaningful. The positive family history group had higher frequencies than the negative family history group in HLA DR3. These differences, however, failed to reach statistical significance when P values were corrected.

DISCUSSION

Our study showed a different pattern of frequencies of HLA antigens between Tourette patients group and the normal control. Some antigens were higher or lower in the tourette patients group than in the controls, even though they failed to reach statistical significance when P values were corrected. Among them, HLA A24(9) was noted as it had a lower frequency both in the total patient group and the patient group with family history.

This finding is a little different from previous reports of Comings et al (1982) and Caine et al (1985). They found no HLA associated with Tourette syndrome. Such different or even conflicting findings in HLA study are not rare in psychiatric disorders (Adler et al. 1985). These differences have been attributed to differences in study methods, sample size or population characteristic in sex, age or ethnicity. Even in Koreans, the data of Kim et al (1986) on HLA typing in normal subjects is not quite the same as that in this study.

Various diseases have been associated with HLA. For example, ankylosing spondilitis has been associated with HLA B27 and rheumatoid arthritis with HLA DR4 (Tiwari and Terasaki 1985). In our study HLA A11, A24(9) 26(10) and B13 were suggested to be associated with Tourette disorder. Some HLA types have been associated with multiple sclerosis, schizophrenia and manic depressive psychosis (Tiwari and Terasaki 1985).

Diseases associated with HLA antigen are known to have a characteristic hereditary pattern of distribution but weak penetrance and association with immunologic abnormalities. Tourette disorder is a genetic disorder (Robertson 1989; Kurlan 1989; Pauls et al. 1990) and has been reported to be associated with some immunologic abnormalities. Bruun (1984) reported that symptom exacerbation was often associated with seasonal allergy responses and ingestion of allergens in food. Rapp (1986) and Mandell (1986) also reported exacerbation of Tourette symptoms on exposure to allergens. In Korean patients, symptoms of Tourette syndrome were aggravated with cold-like illness and fever (Min and Lee 1986). Taken together with these notions, our population study suggests the possibility that Tourette disorder is associated with some of the HLA. However, further studies are needed to investigate the genetic relationship, including a family study which can demonstrate the linkage between a gene marker within the HLA complex and the susceptibility gene of Tourette disorder. If not a genetic linkage study, studies are needed to investigate what kind of HLA are associated with any clinical or pathophysiological parameter of Tourette disorder.

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