HLA ANTIGEN FREQUENCY IN ENDEMIC TROPICAL SPRUE

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Abstract

Twenty-six patients with endemic tropical sprue, diagnosed by strict diagnostic criteria, and 120 normal healthy individuals of the same ethnic group were studied for their HLA-A and -B locus antigen profiles. There was a significant increase in the frequency of HLA-B8 in the disease group (P<0.025) with a relative risk of 2.9. There was a significant increase in the frequencies of HLA-A1, A28 and Bw35 (corrected P<0.03) in the patient group, and A28 and Bw35 was not detected in any of the patients. In view of the reported significance of HLA-B8 as a marker for a generalised immunological hyperresponsive state, a possible auto-immune component in the aetiology of tropical sprue has been suggested. (Indian J Gastroenterol 1983; 2:12-13)

Key words: endemic tropical sprue, HLA antigens, auto-immune.

Introduction

The aetiological factors suggested in the pathogenesis of tropical sprue are (i) nutritional deficiency (ii) a transmissible infectious agent or (iii) presence of a dietary toxin. None of these factors, however, has been found to have a definite causal relationship.

In coeliac disease, a condition somewhat akin to tropical sprue, gluten ingestion has been proved to be the environmental causative factor and genetic susceptibility is strongly indicated by its frequent association with histocompatibility (HLA) antigens B8, DR3 and DR7. There has been no study so far on genetic factors in tropical sprue. In the present study, therefore, the HLA profile of patients with endemic tropical sprue was compared to that of the normal population, in order to detect if a genetic factor in the aetiology exists.

PATIENTS AND METHODS

Patients

Twenty-six North Indian patients with endemic tropical sprue were included in this study. The diagnosis of tropical sprue was established by at least two out of the three following tests for malabsorption being found abnormal.

(i) 24 hour faecal fat content estimated on stools collected on 3 consecutive days. The patients were on 75 g. fat diet for 4 days before and on all three days of stool collection (Normal <6 g).

(ii) Urinary d-xylose excretion (%) was assessed in 5 hours urine sample collected after feeding 5 g. of d-xylose orally. Normal values are less than 1 g. of urinary excretion in 5.

(iii) 24 hour urinary excretion of Co~77~—Vitamin B12 was done by the method of Schilling~7~. (Normal >8%).

In addition to malabsorption, most of the patients had villous abnormalities consistent with tropical sprue and they all responded to treatment with broad spectrum antibiotics and folic acid. Seven of the 26 patients also had relapses, which were treated satisfactorily with the same drugs. Parasitic infections were excluded by stool examination on 3 consecutive days.

HLA typing

The HLA antigens were identified by the standard two stage microlymphocytotoxicity test. Antisera detecting 13 antigens of the A locus and 17 antigens of the B locus were used in the tests. The antigen frequencies in the patient group were compared with those of 120 healthy adult volunteers of the same ethnic group using the x2 test and the level of significance corrected for the number of antigens tested. The relative risk (RR) for the significant associations was calculated by the formula:

Antigen-positive patients x Antigen-negative controls

RR:

Antigen-negative patients x Antigen-positive controls

The value for linkage disequilibrium (LD) and its level of significance 't' was also calculated.

Results and Discussion

Our data on HLA antigen frequencies in 26 cases with endemic tropical sprue and 120 healthy controls (Table) shows a significant increase in the frequency of HLA-B8 (P<0.025, RR=2.9) in patients with a concomitant significant decrease in HLA-Bw35 (P<0.001, RR=0.14). This latter decrease was significant even after correction for the number of antigens tested (P<0.03),
An increased frequency of HLA-B8 has been reported in a variety of conditions considered to be of autoimmune aetiology e.g. chronic active hepatitis, gluten sensitive enteropathy, myasthenia gravis, thyrotoxicosis, idiopathic Addison's disease. It has been suggested that the HLA antigen B8 may be a marker for a state of generalised immunological hyperresponsiveness. In view of the high frequency of HLA B8 in patients in this study, we would like to suggest a possible autoimmune basis for the aetiology of this condition. This being the first study of HLA in tropical sprue, larger experience will help to confirm this association.

The antigen frequencies of HLA A1 and A28 was significantly lower in the patient group (P<0.025 and P<0.005 resp.) with a highly significant elevation in the number of blanks (P<0.0005). The decreased frequency of HLA-A1 in the presence of increased frequency of HLA-B8, needs some comment in view of the known strong positive linkage disequilibrium that exists between these two antigens in Caucasians. This, however, does not hold true for Indian population where the strongest linkage is found between A1 and B17. This has been reported in South Indians studied at Karigiri and in Indian Hindus studied in United States of America. The antigen found in linkage with B8 was A10 in both these studies. Our own unpublished data show in LD of 25 (t-2.17) for A1-B17 and LD of 36.2 (t=3.26) for A10-B8 and no linkage between A1 and B8. Hence, no great emphasis should be laid on the negative correlation between A1 and B8 in the patient group.

### References

8. Mittal KK, Standardization of the HLA typing methods and reagents. Vox Sang 1978; 34:58-63

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**Table**: Phenotype frequencies of the HLA antigens of loci A and B in N. Indians with and without endemic tropical sprue

<table>
<thead>
<tr>
<th>HLA Antigen</th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype frequencies (%)</td>
<td>120</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>22.3</td>
<td>7.7</td>
<td>&lt;0.025</td>
<td>0.27</td>
</tr>
<tr>
<td>A2</td>
<td>26.6</td>
<td>26.9</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>19.2</td>
<td>15.4</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A9</td>
<td>22.5</td>
<td>26.9</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A10</td>
<td>11.7</td>
<td>7.7</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A11</td>
<td>36.7</td>
<td>23.1</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A19</td>
<td>2.3</td>
<td>0.0</td>
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</tr>
<tr>
<td>A28</td>
<td>15.0</td>
<td>0.0</td>
<td>&lt;0.0005</td>
<td>0.21</td>
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<tr>
<td>A30</td>
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<td>ns</td>
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<td>ns</td>
<td></td>
</tr>
<tr>
<td>A32</td>
<td>2.5</td>
<td>3.8</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>A33</td>
<td>5.8</td>
<td>0.0</td>
<td>ns</td>
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<tr>
<td>Blank</td>
<td>25.0</td>
<td>88.5</td>
<td>&lt;0.0005</td>
<td></td>
</tr>
</tbody>
</table>

ns = Not significant
b = P-value after correction < 0.03