HLA B8 and granuloma formation in Crohn’s disease

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SUMMARY In a retrospective survey, patients with Crohn’s disease who were HLA B8 were found to have significantly fewer granulomas in rectal biopsies (p<0.002) and in resected bowel specimens (p<0.02) than non-HLA B8 patients. No statistically significant difference was found between HLA B12 and non-B12 patients. This in vivo evidence of differing immune response capabilities between HLA B8 and non-HLA B8 individuals is compatible with previously reported in vitro studies. Despite these differences, the clinical manifestations and disease course of the two groups of patients was similar, suggesting that neither the presence of HLA B8 nor the development of granuloma directly influence the course of Crohn’s disease.

A number of immunological abnormalities have been reported in patients with Crohn’s disease, but none offers a unifying hypothesis to explain the pathogenesis of the disorder. Defects of immunoregulation have been reported in Crohn’s disease,1 but, in contrast with other conditions in which such defects are considered to be of pathogenetic importance — for example, systemic lupus erythematosus and chronic active hepatitis — there is no association with HBA B8 or DW3. In these, and other putative autoimmune conditions, it has been postulated that the associated genes are in linkage disequilibrium with another gene coding for some aspect of immunoregulation.2,3

There is evidence from clinical studies in conditions such as systemic lupus erythematosus and chronic active hepatitis that HLA B8, DW3 and perhaps B12 may also be of prognostic significance.4,5 HLA phenotype may also influence the response to infections as the type of leprosy developing in family members is HLA-linked.6 Moreover, there is preliminary evidence linking HLA B8 and B12 and defects of immunoregulation in asymptomatic individuals.7,9 We postulated that, if immunoregulation is of pathogenetic importance in Crohn’s disease, and if HLA B8 or B12 is associated in some way with defective immunoregulation, patients with Crohn’s disease who are HLA B8 might have different clinical manifestations from those with other haplotypes. To investigate this possibility, we have analysed selected clinical data of patients with proven Crohn’s disease and correlated the findings with the presence of certain HLA phenotypes.

Methods

PATIENTS

The records of 82 patients with Crohn’s disease who had been typed for A and B tissue antigens were reviewed. All were attending one clinic. Details of sex, age of onset and duration of the disease, number of surgical operations, and the frequency of common extraintestinal complications and treatment requirements were recorded. Rectal biopsies were available from each patient and were classified as either normal or abnormal and the presence or absence of granulomas was noted. Each biopsy was reported without knowledge of the patient’s HLA status. These biopsies were all processed in one laboratory and multiple sections had been reviewed specifically looking for granulomas to help to differentiate between Crohn’s disease and ulcerative colitis. All available resected bowel specimens were also reviewed with respect to the presence or absence of granulomas. The Chi-squared test with Yates’s correction factor was used for statistical analysis unless otherwise indicated. Only these predetermined groups were analysed and probability values of less than 5% were considered to be significant.
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Results

The results are summarised in the Table, which compares patients who are HLA B8 or HLA B12 with those who have neither of these antigens. No statistical difference was found between the HLA B12 patients and the non-B12 or B8 patients. Although nine of the 19 patients who were HLA B8 were found to have at least one abnormal rectal biopsy, none of these was reported to have shown granulomas. In contrast, 15 of the 17 patients with at least one abnormal rectal biopsy out of the total of 42 who were neither HLA B8 or B12 positive were found to have granulomas. The difference between these two groups was highly significant. (p<0.002). Three of 10 HLA B12 patients with abnormal rectal biopsies were found to have granulomas, and, if these patients were combined with the non-B8 or B12 patients, the incidence of granulomas in abnormal rectal biopsies was also significantly greater than the HLA B8 patients (<0.005). Only one out of 10 available resected bowel specimens from HLA B8 patients was reported to show granulomas, whereas granulomas were found in five of nine HLA B12 patients and nine of 13 of the individuals possessing neither of these tissue antigens. The incidence of granulomas in resections from HLA B8 patients was significantly less than in the non-HLA B8 patients (p<0.02). There were no other statistically significant differences between the groups, although the HLA B8 patients tended to have undergone more frequent surgery. Only six patients had presented with the disease under the age of 15 years, and none of these was HLA B8 or B12.

Discussion

Previous studies of HLA in Crohn's disease have been restricted to group analysis10-17 and only HLA B27 has been associated with a specific complication – namely, sacroiliitis.13 This study was in part precipitated by the reported association of HLA B8 with a favourable prognosis in patients with sarcoidosis,18 a disease with many histological similarities to Crohn's disease. In sarcoidosis there is evidence to suggest that HLA B8 patients present acutely but are less likely to develop chronic disease than non-HLA B8 patients.18 Although our study is retrospective and the biopsy interpretation liable to sampling error, the observation that HLA B8 individuals appear to be less able to form granulomas is of interest. The formation of granulomas is part of the host defence mechanism against antigens and may be an important factor in the pathogenesis of Crohn's disease.19 Previous studies have suggested that patients with Crohn's disease who have multiple granulomas are less likely to undergo further surgery than those patients who have few granulomas,20 21 a finding compatible with the tendency of the HLA B8 patients in this study to have undergone more resections. The number of granulomas present in the resected specimens may depend on both the duration of the disease and the site of the biopsy,20 factors which cannot be controlled in the retrospective study such as this, although the groups were approximately similar on both counts. There were no other differences between the groups and it is noteworthy that even those extragastrointestinal complications thought to be immunologically mediated were no more common in HLA B8 or B12 patients than in other patients. The observation that HLA B8 is not increased in frequency in young patients is further evidence that HLA B8 does not influence the course of the disease.

In conclusion, HLA B8 patients with Crohn's disease appear to be less able to form granulomas than those patients who are non-HLA B8. This finding provides in vivo evidence of differing immune responses in HLA B8 patients with Crohn's disease. Although the relevance of granuloma formation is not known, particularly as to whether it represents increased or decreased immune function, the results suggest that HLA B8 patients have an altered ability to respond to antigens. These findings

<table>
<thead>
<tr>
<th>Table</th>
<th>Details of three groups studied</th>
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<tbody>
<tr>
<td></td>
<td>B8</td>
</tr>
<tr>
<td>No. of patients</td>
<td>19</td>
</tr>
<tr>
<td>M - F ratio</td>
<td>10:9</td>
</tr>
<tr>
<td>Age of onset (yr)</td>
<td>28±9</td>
</tr>
<tr>
<td>Duration of disease (yr)</td>
<td>9±9</td>
</tr>
<tr>
<td>No. undergoing resective surgery</td>
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</tr>
<tr>
<td>Total</td>
<td>(No.) (%</td>
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<tr>
<td>Twice or more</td>
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<tr>
<td>Treatment</td>
<td></td>
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<tr>
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<td>Colon only</td>
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<td>Both</td>
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<td>Extraintestinal manifestation</td>
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<tr>
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<td>5</td>
</tr>
<tr>
<td>Anal fissure or fistula</td>
<td>7</td>
</tr>
<tr>
<td>Erythema nodosa</td>
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</table>

p <0-002 (Fisher's exact test).
are compatible with previous preliminary in vitro observations, suggesting that HLA B8 is associated with defects of immune regulation. The association is likely to be an indirect one, possible due to linkage with a gene responsible for this aspect of immunoregulation, and may be stronger if other antigens are studied (particularly DW3, which is in linkage disequilibrium with HLA B8). Although our findings need to be confirmed, preferably in prospective studies, they would suggest that the presence of such an inherited defect does not directly affect the course of the disease.

References

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