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# Studies of HLA-ABC and DR Antigens in Pure Atopic Dermatitis and Atopic Dermatitis Combined with Allergic Respiratory Disease

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The HLA-ABC antigens were investigated in 29 patients with pure atopic dermatitis and 43 patients with atopic dermatitis combined with atopic respiratory disease (ARD). Furthermore, the DR antigens were studied in 10 patients with dermatitis alone and in 24 patients with combined atopic disease. The frequencies of antigens and the HLA phenotypes A1,B8 and A3,B7 in the entire group of patients and in two subgroups did not differ significantly from those in controls, when correction was made for the number of comparisons made. However, the frequency of HLA-DR7 was strikingly low, but this observation needs confirmation. IgE levels were measured in eight patients with pure dermatitis and in 24 patients with dermatitis combined with ARD and found equally increased in both groups compared to controls. *Key words: Atopic dermatitis; Atopic respiratory disease; Subgroups; HLA antigens.*

Atopic dermatitis (AD) is a skin disorder with characteristic clinical features and a chronic remitting course. Though the etiology is uncertain, AD is associated with both humoral and cellular immunological abnormalities (1). Dermatological and/or respiratory atopy occur in about 50–70% of first degree relatives, indicating the involvement of genetic factors. Because of the immunologic abnormalities, it might be assumed that some of these genetic factors belong to the HLA system which controls various immune responses. In spite of numerous studies, however, the role of the HLA system in atopic disease remains uncertain. Thorsby et al. (2) found an increased frequency of the phenotype A1,B8 in children with allergic asthma and this finding was confirmed by Soothill et al. (3). In a subsequent analysis of subgroups of patients with atopic dermatitis or respiratory atopy alone the same investigators (4) reported that the HLA phenotype A1,B8 was most frequent (36%) in eczema complicated by asthma and/or hay fever and least frequent (5%) in hay fever alone compared to the frequency in the controls (17%). Krain & Terasaki (5) and Desmons et al. (6) could not confirm these findings but found slightly increased frequencies of A3 and A9, and B12, Bw5 and Bw15 respectively.

Hyperglobulinemia of IgE is a frequent but not obligatory finding in AD. Elevated serum IgE levels are most usually observed in patients with AD combined with allergic respiratory disease (ARD) (7). Turner et al. (8) failed to show association between the HLA phenotypes A1,B8 and A3,B7 and IgE antibody levels in four clinically defined subgroups of atopic patients. Marsch et al. (9) recently reported a strong association between HLA-Dw2 and the immune response to short ragweed pollen allergen Ra5. The present study represents an attempt to clarify the situation for a possible association between AD and HLA in relation to the clinical subtypes of pure AD versus AD combined with ARD. In addition we represent the first report of DR typing in AD.

## PATIENTS

Seventy-two patients with moderate and severe atopic dermatitis (AD) since early childhood were studied. The diagnose was established by the criteria of Hanifin & Rajka (10) and in all cases, disease severity had caused hospitalization in dermatology wards at least once. In 29 patients (group I), AD

was the only atopic manifestation. In 43 patients, a respiratory atopic disease was present in addition to AD (group II). Twenty-four of these suffered from bronchial asthma, twelve from hay fever or allergic rhinitis and seven from both asthma and hay fever. A family history of atopic disease in 1st degree relatives was present in 8 patients (28%) of group I and in 27 patients (63%) of group II. The age range at the time of the study was 2–54 years (mean 26) in group I and 3–51 years (mean 22) in group II.

## METHODS

HLA-typing for 13 HLA-A, 20 HLA-B, 5 HLA-C, and 7 HLA-DR antigens was carried out as described earlier (11). Antigen frequencies in the patients were compared with those in 426–3301 unrelated healthy Danish controls by means of Fisher's exact test. *P*-values were corrected for the number of comparisons made as indicated in the tables. The method of Haldane (12) was used for combined calculations. Serum IgE was measured by the radio immuno sorbent technique in twelve patients from group I and in 24 patients from group II. Eosinophils in venous blood were counted in 15 patients from group I and in 30 patients from group II.

## RESULTS

No association between HLA-ABC series antigens and any of the groups was found. In particular, the antigens previously reported to be associated with AD had normal frequencies (Table I). However, studies of the frequencies of the phenotypes A1,B8 and A3,B7

Table I. *HLA-ABC antigens in AD with and without ARD*

No significant differences between patient groups and controls

| | Frequency (%) | | |
|---|---|---|---|
| HLA phenotype | AD-ARD ($n$=29) | AD+ARD ($n$=43) | Controls ($n$=3301) |
| A3 | 21 | 28 | 28.3 |
| A9 | 18 | 16 | 17.3 |
| B5 | 10 | 12 | 10.2 |
| B12 | 38 | 23 | 26 |
| B15 | 21 | 19 | 18.4 |
| A1,B8 | 17 | 19 | 19.1 |
| A3,B7 | 10 | 18 | 12.2 |

Table II. *HLA-DR in AD with and without ARD (Svejgaard et al., 1984)*

| HLA-DR antigen | AD-ARD ($n$=10) | AD+ARD ($n$=24) | All patients ($n$=34) | Hyper IgE ($n$=23) | Controls ($n$=704) |
|---|---|---|---|---|---|
| DR1 | 0 | 13 | 9 | 4[b] | 19.3 |
| DR2 | 50 | 29 | 35 | 44 | 28.3 |
| DR3 | 30 | 33 | 32 | 44 | 25.9 |
| DR4 | 40 | 33 | 35 | 30 | 34.7 |
| DR5 | 30 | 13 | 18 | 13 | 11.7 |
| DR7 | 0 | 8 | 6[a] | 4[c] | 28.9 |
| DRw8 | 0 | 8 | 6 | 9 | 8.7 |

[a] $p$=0.02, [b] $p$=0.05, [c] $p$=0.03. None of these remained significant after correction.

respectively (Table I) showed neither differences between the clinical subgroups nor between patients and controls. Because of this inconsistency between our findings and those of Turner et al. (4), we performed combined calculations on the individual HLA-A and B antigen data from the two studies. In these calculations we used patient HLA data kindly submitted to us by Turner (personal communications) and for these English data we used control frequencies from Bristol as tabulated in Ryder et al. (13).

Comparisons were made separately for AD patients with and without respiratory allergy. Tendencies to increased frequencies were seen of A11 in patients with dermatitis alone and of B12 in patients with dermatitis combined with ARD, but they were clearly without significance (results not shown).

Studies of the DR antigens was carried out in 34 patients and the results are shown in Table II. Compared to the control group, the frequency of the DR7 antigen was significantly decreased in the total group of patients ($p=0.02$). This was also the case in the group of 23 patients with elevated IgE serum levels ($p=0.03$) and in this group DR1 appeared to be decreased, too ($p=0.05$). However, the significance of these deviations disappeared when correcting the $p$-values for the number of comparisons made. IgE levels ranged from 15–15 000 u/l (normal 3–263 u/l) with a median of 2 440 u/l in group I. In group II range values were 145–9 500 u/l and the median was 2 125 u/l (Table III). Eosinophile cell counts (upper normal limit 350 mill/l) showed ranges of 150–994 mill/l and 269–3 156 mill/l, and median values of 469 mill/l and 788 mill/l in groups I and II respectively (Table IV).

Table III. *Serum IgE levels in 36 patients with atopic dermatitis with and without allergic respiratory disease*

| Group | No. | IgE levels[a] Median (range) |
|---|---|---|
| AD without ARD | 12 | 2 440 (15–15 000) |
| AD with ARD | 24 | 2 125 (145–9 500) |
| AD with hay fever | 9 | 1 000 (145–5 600) |
| AD with asthma | 11 | 3 400 (175–9 500) |
| AD with hay fever & asthma | 4 | 4 710 (4 450–8400) |

[a] Radio Immuno Sorbent Test, kilo (international units)/l, normal adults <263.

Table IV. *Eosinophile cell counts in 45 patients with atopic dermatitis with and without allergic respiratory disease*

| Group | No. | Eosinophile cell count[a] Median (range) |
|---|---|---|
| AD without ARD | 17 | 469 (150–994) |
| AD with ARD | 30 | 788 (269–3 156) |
| AD with hay fever | 8 | 525 (263–1 100) |
| AD with asthma | 16 | 922 (369–2 113) |
| AD with hay fever & asthma | 6 | 1 047 (469–3 156) |

[a] Normal <350 mill/l.

## DISCUSSION

Our results do not confirm previous observations of associations between the HLA-system and atopic dermatitis. We found no apparent differences in the distribution of the HLA-ABC antigens including certain phenotype combinations between the total patient group or any of the subgroups, viz. pure AD, AD combined with ARD and AD with hyper IgE, and the controls.

Six patients, who at the time of examination was below 10 years of age presented at that time with pure AD. At the follow-up 5–10 years later, four of these had developed hay fever or asthma and consequently were allocated to the other subgroup. Reasons for these disagreements may in some cases be due to different ways of ascertainment and definition and subgrouping of the disease (5). In several studies the sizes of the investigated group and subgroups are relatively small (4). Weak associations require large studies of patients to be confirmed. Significant associations in some studies loose the significance, when corrected for number of antigens studies (4). Finally, the occurrence of related patients in a group bias the distribution of antigens and blurs the result (6). An increased A1,B8 phenotype frequency in patients with multisystem atopy characterized by eczema, hay fever and asthma was found by Turner et al. (4) suggesting a difference between this disease pattern and later onset atopy as hay fever or asthma alone. A1,B8 was found in one of our seven patients with AD combined with asthma and hay fever, a finding not supporting this hypothesis. More studies are needed regarding this subgroup. Further evidence for HLA as a genetic factor in AD has been looked for in family studies by among others Desmonds et al. 1976 (6). They were not able to demonstrate associations to A1,B8 but to single antigens as mentioned. MacKie & Dick (14) found an increased incidence of A1,B8 (30%) and A2,B12 (40%) in 17 probands of a family study comprising 89 patients, siblings and parents from 17 families. However, they found no close link between these findings and clinical expression of atopy. Fourteen siblings shared identical haplotypes with diseased patients without showing clinical evidence of disease. Two families had each two affected siblings, none of whom were HLA identical.

Our HLA-DR studies did not reveal any strong associations either. The decrease of DR7 in the total patient group and of DR7 and DR1 in the hyper IgE group were not significant when corrected for number of antigens studied. Thus more studies are needed if DR associations must be excluded.

Serum IgE values were compared between patients with AD alone and patients with AD combined with ARD. We were not able to confirm previous observations (7, 15) that patients with eczema alone have lower serum IgE levels. The IgE values were measured during periods of exacerbation of the atopic dermatitis and were not available for all patients. It is possible that the IgE concentration fluctuates with the severity of dermatitis, which might explain the discrepancy between one and other observations.

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