Increased Frequency of HLA-DR11 in Pediatric Human Immunodeficiency Virus-Associated Parotid Gland Enlargement

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We sought to determine whether an increased frequency of the HLA-DR11 (formerly DR5) phenotype is found in human immunodeficiency virus (HIV)-infected children with parotid gland enlargement. In HIV-infected adults, parotid gland enlargement may be part of the diffuse infiltrative CD8 lymphocytosis syndrome. An increased frequency of expression of HLA-DR11 has been described in association with diffuse infiltrative CD8 lymphocytosis syndrome. We conducted a case-control study with 26 HIV-infected children, 13 of whom had parotid gland enlargement and 13 of whom did not but who were matched for age, race, and sex with those with parotid gland enlargement. Clinical and laboratory parameters (including HLA-DR11 phenotype) were compared between the two groups. HIV-positive children with parotid gland enlargement showed an increased frequency of HLA-DR11, similar to their adult counterparts with diffuse infiltrative CD8 lymphocytosis syndrome. The HLA-DR11 phenotype may be associated with the development of parotid gland enlargement in HIV-infected children and may be a marker for a more benign outcome of HIV infection.

Parotid gland enlargement (PGE) associated with human immunodeficiency virus (HIV) infection was first noted in HIV-infected children in 1983 and in HIV-positive adults in 1985 (4). PGE is now recognized as a common, early sign of pediatric HIV infection and is included in the Centers for Disease Control and Prevention’s (CDC’s) classification of mild signs associated with HIV infection (3). An increased frequency of expression of the HLA-DR5 phenotype (now designated HLA-DR11 by the 11th HLA Workshop [16]) has been described in association with PGE in the diffuse infiltrative CD8 lymphocytosis syndrome (DILS) found in black HIV-infected adults (9, 16). This HLA predilection may indicate a heightened immune response and protection from HIV disease progression (11).

To determine if children with HIV-associated PGE also show an increased frequency of expression of HLA-DR11, we studied 26 HIV-positive children: 13 with PGE (PGE+) and 13 others without PGE (PGE−) who were matched for age, race, and sex with those with PGE. To further elucidate the relationship of pediatric PGE to adult DILS, we also compared the clinical and immunologic parameters of these PGE+ and PGE− children.

**MATERIALS AND METHODS**

**Patient profiles.** A total of 26 HIV-positive children (identified by an HIV-specific enzyme-linked immunosorbent assay and confirmed by Western blot [immunoblot] analysis; ages, 2 to 13 years; mean age, 7.34 ± 2.98 years) were studied after obtaining informed consent. Study subjects with PGE were recruited from the Pediatric Immunology Clinic of Schneider Children’s Hospital. Control subjects without PGE matched for age, race, and sex with those with PGE were also recruited from the Pediatric Immunology Clinic. Thus, each group consisted of 4 males and 9 females as well as 9 blacks, 2 Caucasians, and 2 Hispanics. HIV transmission was predominantly via the perinatal route in both the PGE+ and the PGE− groups.

**Laboratory evaluation.** Class II HLA phenotyping was performed by the complement-dependent cytofluorocytometry method as described previously (1, 18). We also compared the following laboratory characteristics of PGE+ and PGE− HIV-infected children: (i) cell surface immunophenotypes of the peripheral blood lymphocytes as determined by flow cytometry, (ii) Epstein-Barr virus (EBV)-specific humoral responses (SmithKline Bioscience, Syosset, N.Y., or Roche Biomedical Laboratory, Great Neck, N.Y.), (iii) radiographic evidence of lymphoid interstitial pneumonitis, and (iv) total amylase levels by enzymatic and column chromatography.

**Statistics.** Comparisons between patient groups were performed by paired t test or Wilcoxon signed rank test for continuous variables. Fisher’s exact test or the chi-square test were used to compare categorical variables. Relative risks and odds ratios were calculated.

**RESULTS**

**Clinical profile.** A total of 13 PGE+ HIV-infected children were studied (Table 1). All children had bilateral, nontender, multiple intraparotid masses over a period of at least 6 months. The average age of onset was 6.62 ± 3.13 years. None of the PGE+ patients had associated sicca complex. Children in the PGE+ group had a statistically higher incidence of cervical lymphadenopathy (77%) compared with PGE− (15%) children, but the incidence of lymphoid interstitial pneumonitis, sinusitis, or opportunistic infection did not differ between the groups. In addition, two PGE+ subjects were found to have thymic cysts, one by biopsy and one radiographically. By the CDC classification, PGE+ subjects had milder disease severity (most patients were CDC class A) than PGE− children. However, no significant differences in infectious complications, opportunistic infections, hospital admission rates, or mortality were found between the groups.

**Laboratory evaluation.** Eight of 13 (62%) PGE+ subjects (62%) were positive for the HLA-DR11 phenotype, whereas 2 of 13 (18%) PGE− children were positive for the HLA-DR11 phenotype (P = 0.04; Fisher’s exact test, two-sided; odds ratio, 8.8). The estimated relative risk of PGE conferred by HLA-DR11 is 4.0. Of the eight HIV-infected children expressing the HLA-DR11 phenotype, five (62%) were black, two (25%) were Caucasian, and one (12.5%) was Hispanic. The prevalence of the HLA-DR11 phenotype in the general black, Caucasian, and Hispanic populations is 18.1, 17.0, and 18.1%, respectively (Ono Lambda, Inc.). Thus, the prevalence of the
The HLA-DR11 phenotype in the black HIV-positive pediatric population is significantly increased compared with that in the general black population (P = 0.0034; tested by goodness of fit by chi-square analysis).

The immunologic profiles of patients with HIV-associated PGE and patients without PGE are presented in Table 1. Absolute CD4+ T-lymphocyte counts were significantly higher in PGE+ children (768.2 ± 473.2 versus 390.8 ± 372.1), but there was no significant difference in the percentage of CD4+ T cells, absolute number of CD8+ T cells, or percentage of CD8+ T cells between the groups. No significant differences in amylase levels or EBV seropositivity were found between the groups.

### DISCUSSION

The etiology of parotid gland enlargement associated with HIV infection is unclear. Possible mechanisms include direct infection by HIV or other viruses such as EBV or cytomegalovirus, immunologic dysfunction associated with HIV (polyclonal B-cell activation), or an aberrant immune response to self-antigens such as salivary tissue (8, 13, 14, 17). In situ hybridization studies have failed to demonstrate the EBV genome within lesions, but they have shown the presence of HIV RNA within focal areas of the mononuclear cell infiltrate of biopsy specimens, presumably representing HIV-infected lymphocytes (2, 6). However, HIV RNA has not been demonstrated within salivary gland epithelia of HIV-infected adults (17). Our study demonstrated no differences in EBV seropositivity between PGE+ and PGE− subjects, implying that EBV infection does not play a role in the development of PGE.

This study also demonstrated distinct differences between PGE in HIV-infected children and DILS found in HIV-infected adults. As in HIV-infected adults with DILS, HIV-positive children with PGE commonly have cervical lymphadenopathy, lymphoid interstitial pneumonitis, an increased incidence of HLA-DR11, and more benign HIV disease, as evidenced by the greater CD4+ lymphocyte counts and the greater prevalence of children with mild symptoms. However, the absence of sicca complex, the presence of recurrent bacterial infections such as sinusitis, and the lack of CD8+ T-cell lymphocytosis distinguish HIV-infected children with PGE from their adult counterparts. Such differences may indicate differences in the immunologic responses of children to HIV infection compared with those of adults.

The significance of an increased frequency of expression of the HLA-DR11 phenotype in HIV-infected adults and children with PGE remains unclear. Clear associations exist between certain HLA alleles and autoimmune disease, and recent studies have identified an association between specific HLA class II alleles and milder outcome of viral infections such as hepatitis B and hepatitis C (12, 15). However, past studies have also associated this phenotype with both mild and advanced HIV infection (5, 7). Similarly, other HLA allotypes have been associated with other pathogenic features of adult HIV infection. For example, HLA DR3 and DQ2 have been found at an increased frequency in patients with opportunistic infections. DR1 has been associated with Kaposi’s sarcoma, and DQ2 has been associated with synctium-inducing variants of HIV type 1. Select class I major histocompatibility complex phenotypes have also been associated with certain HIV-related signs or symptoms. HLA-B35 has been found in subjects displaying a rapid decline in CD4+ T lymphocytes, and B62 has been associated with prodromal fever and rash (10). In our study, PGE+ children had milder HIV disease according to the CDC classification and increased CD4+ T-lymphocyte counts compared with PGE− children, but the two groups did not differ significantly in terms of disease course. However, detection of survival differences between HIV-infected children with and without PGE will require long-term follow-up of large numbers of these children.

### REFERENCES


### Table 1. Laboratory features of HIV-infected children with and without PGE

<table>
<thead>
<tr>
<th>Patient group</th>
<th>CD4+ T cells</th>
<th>CD8+ T cells</th>
<th>Amylase level</th>
<th>No. (%) EBV seropositive/no. tested (%)</th>
<th>No. (%) HLA-DR11 positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ T cells</td>
<td>Absolute no. (cells/mm³)</td>
<td>%</td>
<td>Absolute no. (cells/mm³)</td>
<td>%</td>
<td>U/liter</td>
</tr>
<tr>
<td>PGE+ (n = 13)</td>
<td>768.2 ± 473.2</td>
<td>23.6 ± 9.9</td>
<td>1,220.5 ± 653.4</td>
<td>45.0 ± 15.1</td>
<td>1.99 ± 1.66</td>
</tr>
<tr>
<td>PGE− (n = 13)</td>
<td>390.8 ± 372.1</td>
<td>18.7 ± 12.5</td>
<td>880.5 ± 723.4</td>
<td>45.5 ± 15.2</td>
<td>2.02 ± 1.09</td>
</tr>
</tbody>
</table>

* Boldface indicates a significant P value.  
* a Paired t test.  
* b Fisher’s exact test.