Lack of Association Between HLA Antigen DR3 and $\alpha_1$-Antitrypsin Deficiency in Liver Transplant Recipients

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The relationship between $\alpha_1$-antitrypsin deficiency ($\alpha_1$-ATD) and the HLA antigen system was studied in 32 liver transplant recipients. Despite previous reports of an association of HLA antigen DR3 with homozygosity for $\alpha_1$-AT ZZ, no such association was seen in this population of $\alpha_1$-ATD homozygous ZZ patients with advanced hepatic disease. Thus, the reported association of HLA class II antigens and homozygosity for the Z allele for $\alpha_1$-AT may be an artifact of either a small study population or geographic inbreeding and a coincidental association of certain HLA antigens with the presence of homozygosity for the Z allele of $\alpha_1$-AT.

KEY WORDS: HLA antigen; $\alpha_1$-antitrypsin; liver transplant.

Liver transplantation is a life-saving therapy for individuals with end-stage liver disease for whom medical therapy does not exist (1–7). These individuals by definition represent the worse cases. Should an association between the presence of a given liver disease and certain HLA antigens exist, such an association would be expected to be readily demonstrable in individuals with the most severe disease, such as those requiring liver transplantation. The demonstration of such an association in liver transplant recipients with a given disease would be expected to occur as a result of a selection bias in which the more severely diseased cases are identified and selectively referred for transplantation. Therefore, in order to either confirm or refute the reported association between HLA antigen DR3 with $\alpha_1$-ATD (homozygosity for the Z allele), the following study was performed.

MATERIALS AND METHODS

Between January 1, 1980, and December 31, 1990, a total of 2500 liver transplants were performed at the University of Pittsburgh Medical Center (UPMC). Of these, 1888 were adult cases and 612 were pediatric cases. During this time, 47 patients with $\alpha_1$-ATD homozygous ZZ were seen and transplanted. Of this group, 32 (68%) underwent HLA typing prior to their transplant and were utilized for the analysis that follows: 18 were male and 14 were female. Their ages ranged from 10 months to 57 years (mean $15.65 \pm 14.6$).

In each case, the diagnosis of $\alpha_1$-ATD was confirmed by quantitation of the serum $\alpha_1$-AT level and determination of the Pi phenotype and as a result of family studies (8–10).

$\alpha_1$-Antitrypsin Studies. For the quantitative assay, serum levels of $\alpha_1$-AT were quantitated by rate nephelometry using the Beckman Array Protein System (8, 9). Normal levels at UPMC are 85–213 mg/dl. Determination of the $\alpha_1$-AT Pi phenotype was performed using isoelectric focusing on agarose gel (10). Standards were utilized...
in each run. For family studies, whenever possible the patients' siblings, parents, and children were studied to confirm the \( \alpha_1 \)-AT phenotype.

**HLA Typing.** HLA typing was performed using lymphocytes isolated from the peripheral blood of each individual utilizing a standard NIH microlymphocytotoxicity assay and an immunomagnetic fluorescence technique for the DR typing (11, 12).

**Liver Histology.** The pathological findings of the resected livers were characterized grossly and by a histologic examination performed by staff pathologists at Presbyterian University and Children's Hospital of Pittsburgh. The records of these examinations were reviewed.

**Statistical Analysis.** All values are reported as mean ± SEM. Statistical analyses were performed utilizing chi-square analysis; \( P < 0.05 \) was considered significant.

**RESULTS**

Twenty-one children having a mean age of 6.8 ± 3.6 years and 11 adults having a mean age of 32.5 ± 12.8 years with \( \alpha_1 \)-ATD and ZZ phenotype were studied. They represent 0.3% of the children and 0.6% of the adults transplanted at the University of Pittsburgh Medical Center during the 10-year period of this study.

**HLA Antigens.** The prevalence of HLA antigen DR3 in a control group of 200 normal blood donors in Pittsburgh was 22.6%. The prevalence of this antigen in the 32 patients studied as part of this investigation is shown in Table 1. Whether one looks at the cases in adults, children, or all of the cases transplanted for \( \alpha_1 \)-ATD, a reduced prevalence of DR3 was found as compared to a normal control population. None of these differences are significant.

**\( \alpha_1 \)-Antitrypsin Levels.** The serum \( \alpha_1 \)-AT level of these 32 patients as well as those of a group of liver disease controls consisting of 22 adults and 44 children matched for age (two for each case with \( \alpha_1 \)-ATD) also transplanted at the University of Pittsburgh Medical Center during the study period is shown in Table 2. As expected, the patients with \( \alpha_1 \)-ATD had very low levels of the protease inhibitor in their sera prior to OLTx. In contrast, compared to normal controls, the non-\( \alpha_1 \)-ATD cases coming to OLTx had increased serum levels of \( \alpha_1 \)-AT.

**Liver Histology.** The histological findings of the 32 cases studied are reported in Table 3. Of interest is the fact that no case of \( \alpha_1 \)-AT was found to have a cholangiocarcinoma and only one pediatric patient was found to have a hepatoma. These figures stand in contrast to the 2% incidence of hepatocellular carcinoma in adults transplanted for hepatocellular disease other than \( \alpha_1 \)-ATD and the 0.75% rate for all other children coming to OLTx.

**DISCUSSION**

In a study performed by Doherty et al (13), it was reported that DR3 occurs more frequently in patients with \( \alpha_1 \)-ATD having a liver disease, suggesting that in these patients this allele may influence the outcome of the liver disease seen as part of the greater spectrum of \( \alpha_1 \)-ATD disease.

Doubts about such an association in individuals with \( \alpha_1 \)-ATD arose when other groups such as those of Nemeth and Möller (14) could not confirm the association of this allele with development of liver disease in children with \( \alpha_1 \)-ATD.

To resolve this controversy, the present study was initiated. Because of the relative rarity of ho-
mozygous ZZ \( \alpha_1 \)-ATD as a cause of clinical liver disease and because of the large number of HLA antigens that are recognized to exist currently, the present study was biased in favor of finding an association by examining only the HLA antigen present in individuals with \( \alpha_1 \)-ATD coming to OLTx. Specifically, we selected the poorer cases for study. Were an association between certain HLA antigens and \( \alpha_1 \)-ATD liver disease to exist, one would have expected an enrichment of these HLA antigens in a population of individuals with liver disease sufficiently severe as to be referred for liver transplantation. Such would appear to be the case for other liver disease like autoimmune chronic active hepatitis, sclerosing cholangitis, and chronic HBV-related liver disease (15–19). Despite this bias in the accrual of subjects for this study, no association by examining only the HLA antigen DR3 was found in either children or adults or both groups combined having \( \alpha_1 \)-ATD liver disease confirmed by quantitation of the serum \( \alpha_1 \)-AT level, isoelectric focusing for phenotype analysis, and family studies of the probands as well as having a need for OLTx. Therefore, based upon this biased, worst-case population, no association between HLA antigen DR3 and \( \alpha_1 \)-ATD liver disease appears to exist.

REFERENCES

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