Digestive Diseases and Sciences, Vol. 38, No. 8 (August 1993), pp. 1489–1491

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Lack of Association Between HLA Antigen DR3 and α_1-Antitrypsin Deficiency in Liver Transplant Recipients

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The relationship between α_1-antitrypsin deficiency (α_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 α_1-AT ZZ, no such association was seen in this population of α_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 α_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 α_1-AT.

KEY WORDS: HLA antigen; α_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 α_1-ATD (homozygosity for the *Z* allele), the following study was performed.

Manuscript received August 17, 1992; accepted December 28, 1992.

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Aided by Research Grants from the Veterans Administration and Project Grant DK29961 from the National Institutes of Health, Bethesda, Maryland.

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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 α_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 ± 14.6).

In each case, the diagnosis of α_1-ATD was confirmed by quantitation of the serum α_1-AT level and determination of the Pi phenotype and as a result of family studies (8–10).

α_1-Antitrypsin Studies. For the quantitative assay, serum levels of α-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 α1-AT Pi phenotype was performed using isoelectric focusing on agarose gel (10). Standards were utilized

TABLE 1. PREVALENCE OF HLA ANTIGEN DR3 IN PATIENTS COMING TO OLTx FOR α_1-ANTITRYPSIN DEFICIENCY (PI ZZ PHENOTYPE)

	DR3 (%)
Adults (N = 11)	9.0
Children (N = 21)	9.5
Total α_1-ATD (N = 32)	9.4
Pittsburgh controls (N = 200)	22.5

in each run. For family studies, whenever possible the patients' siblings, parents, and children were studied to confirm the α_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 α_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 α_1-ATD, a reduced prevalence of DR3 was found as compared to a normal control population. None of these differences are significant.

α_1-Antitrypsin Levels. The serum α_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 α_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 α_1-ATD had very low levels of the protease inhibitor in their sera prior to OLTx. In contrast, compared to normal controls, the non-α_1-ATD cases coming to OLTx had increased serum levels of α_1-AT.

TABLE 2. α_1-ANTITRYPSIN LEVELS (MEAN VALUES) AT TIME OF OLTx

	α_1-AT (mg/dl)
Adults (N = 11)	38.4 ± 2.3*
Children (N = 21)	34.7 ± 1.8*
Liver disease controls†	200.9 ± 10.8‡
Children (N = 44)	
Adults (N = 22)	
Normal controls (N = 200)	149 ± 6.4

*$P < 0.01$ from both normal controls and liver disease controls.
†Individuals coming to OLTx for conditions other than α_1-ATD.
‡$P < 0.01$ from the normal controls.

Liver Histology. The histological findings of the 32 cases studied are reported in Table 3. Of interest is the fact that no case of α_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 α_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 α_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 α_1-ATD disease.

Doubts about such an association in individuals with α_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 α_1-ATD.

To resolve this controversy, the present study was initiated. Because of the relative rarity of ho-

TABLE 3. FREQUENCY OF HEPATIC CANCER IN 32 CASES STUDIED COMPARED TO THAT OCCURRING IN OTHER TYPES OF CIRRHOSIS

	Cirrhosis (%)	*Hepatoma (%)*	*Cholangiolar CA (%)*
Adults (N = 11) with α_1-ATD	100	0	0
Children (N = 21) with α_1-ATD	100	5	0
Other adults coming to OLTx for PNC	100	2	0
Other children coming to OLTx	0	0.75	0

mozygous *ZZ* α_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 α_1-ATD coming to OLTx. Specifically, we selected the poorer cases for study. Were an association between certain HLA antigens and α_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 between any HLA antigens and particularly DR3 was found in either children or adults or both groups combined having α_1-ATD liver disease confirmed by quantitation of the serum α_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 α_1-ATD liver disease appears to exist.

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