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Survey of HLA Distribution in Patients with End Stage Renal Disease Secondary to Reflux Nephropathy

Reflü Nefropatisine Bağlı Son Dönem Böbrek Hastalığı Gelişen Hastalarda HLA Dağılımının İncelenmesi

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Abstract/Öz

Introduction: To evaluate the human leukocyte antigen (HLA) types of patients with vesicoureteral reflux (VUR) who underwent renal transplantation for end-stage renal disease (ESRD) to investigate for any significant association.

Methods: This retrospective study comprised 26 patients (male, 15; female, 11) with ESRD secondary to VUR (ESRD/VUR group) who underwent renal transplantation, and 38 healthy donors (female, 24; male, 14) were randomized in the control group. The Single Specific Primer-Polymerase Chain Reaction (low resolution) method was performed for HLA typing. The statistical analyses included chi-square test and calculation of odds ratio (OR).

Results: The median age was 25.2 years (R, 10-41) in the ESRD/VUR group and 43.9 (R, 20-76) in the control group. A statistically significant difference between HLA A and B types was not observed. The HLA DRB1*01 was significantly higher in the ESRD/VUR group than in the control group (p=0,024). The OR for the HLA DRB1*01 was 2.727. The risk of developing ESRD secondary to VUR was 2.727 times higher in the presence of the HLA DRB1*01.

Conclusion: An association between HLA DRB1*01 and ESRD secondary to VUR was established. The HLA DRB1*01 antigen could be interpreted as a poor prognostic factor of reflux nephropathy. This finding should be supported by further studies.

Amaç: Vezikoüreteral reflü (VUR) kronik böbrek hastalığı nedenlerinden biridir. Bu çalışmada amaç, reflü nefropatisine bağlı son dönem böbrek hastalığı (SDBH) tedavisinde, böbrek nakli yapılan hastalarda HLA doku antijen tiplerinin değerlendirilmesidir.

Yöntemler: Reflü nefropatisi nedeni ile böbrek nakli yapılan 26 olgunun (15 erkek, 11 kadın) HLA doku antijenleri geriye dönük olarak incelendi. Kontrol grubunu; rastlantısal olarak seçilen 38 (24 kadın, 14 erkek) sağlıklı verici oluşturdu. İstatistiksel analiz ki-kare testi ile yapıldı. Her bir HLA doku antijen tipi için tahmini rölatif risk (Odds ratio-OR) hesaplandı.

Bulgular: VUR grubunun yaş ortalaması 25,2 yıl (10-41 yaş), kontrol grubunun yaş ortalaması 43.9 yıl (20-76 yaş) idi. Gruplara göre HLA doku antijen dağılımı Tablo 1'de gösterilmiştir. HLA A ve B doku tiplerinde çalışma ve kontrol grubunda anlamlı fark saptanmadı. DRB1*01 doku tipi kontrol grubuna göre çalışma grubunda istatistiksel olarak anlamlı yüksekti (p=0,024). Bu antijene ait karşılaştırmada OR 2,727 idi. Bu sonuca göre DRB1*01 doku tipinin varlığında reflü nefropatisine bağlı SDBH gelişme oranı 2,727 kat yüksekti.

Sonuç: Çalışmamızda reflü nefropatisine bağlı son dönem böbrek hastalığı ile DRB1*01 HLA doku antijeni birlikteliği saptanmıştır. Bu veri DRB1*01 HLA doku antijenine sahip VUR'lu olgularda tedavi ve prognozun değerlendirilmesinde kullanılabilir.

Keywords: Vesicoureteral reflux, HLA, renal nephropathy

Anahtar Kelimeler: Vezikoüreteral reflü, HLA, renal

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Introduction

Reflux nephropathy (RN) is one of the causes for chronic kidney disease, and end-stage renal disease (ESRD) may develop in 5% of pediatric patients and 10% of adult patients (1). The factors affecting the development of ESRD secondary to vesicoureteral refluxes (VUR) are renal dysplasia/hypoplasia, urinary tract obstruction, VUR grade, scars, recurrent urinary tract infections, bladder dysfunction, and mismanaged treatment modalities (2). Urinary tract infection associated with VUR, the immunologic response of the patient, and the subsequent cascade of inflammation in the renal parenchyma deteriorates the renal function (3, 4).

Human leukocyte antigen (HLA) tissue antigens are well-defined examples of the diversity of immune system response (4). The donor and recipient's tissue antigens and their compatibility are evaluated before kidney transplantation. HLA compatibility is related to graft vitality and lower immunosuppressant dose requirement after renal transplantation. The relation between HLA-tissue compatibility antigen and ESRD secondary to RN was reported previously in the literature (5-9).

In this present study, we aim to determine the distribution of HLA tissue antigen in patients who underwent renal transplantation secondary to ESRD secondary to VUR.

Methods

Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Approval number: 83045809-604.01.02/06.09.2016). Because the study was retrospective, patient consent was not obtained, and only file data were evaluated. A total of 26 patients (15 male, 11 female) underwent renal

Table 1. Properties and statistical analysis of the two groups

	*ESRD/VUR Group n:26	Control Group n:38	p
Mean Age (year)	25.2(10-41)	43.9(20-76)	-
Male/Female (n)	15/11	14/24	-
**HLA DRB1*01 (n)	4(15.4%)	-	p<0.05

ESRD: end-stage renal disease; VUR: Vesicoureteral reflux; **HLA: Human leukocyte antigen

Table 2. Distribution of HLA A and B tissue antigens

*HLA TYPE	ESRD/VUR GROUP	CONTROL GROUP		
	n (%)	n (%)	p	**OR
A03	5(19.2)	8(21.1)	0.859	0.893
A11	5(19.2)	9(23.7)	0.672	0.767
A23	2(7.7)	3(7.9)	1.000	0.972
A24	6(23.1)	9(23.7)	0.955	0.967
A26	4(15.4)	5(13.2)	1.000	1.200
A30	1(3.8)	2(5.3)	1.000	0.720
A33	2(7.7)	1(2.6)	0.561	3.083
A40	1(3.8)	0(0)	0.406	2.520
A68	2(7.7)	1(2.6)	0.561	3.083
B05	1(3.8)	0(0)	0.406	2.520
B07	1(3.8)	3(7.9)	0.640	0.467
B08	1(3.8)	1(2.6)	1.000	1.480
B13	1(3.8)	1(2.6)	1.000	1.480
B15	1(3.8)	1(2.6)	1.000	1.480
B18	3(11.5)	5(13.2)	1.000	0.861
B27	3(11.5)	1(2.6)	0.295	4.826
B35	11(42.3)	10(26.3)	0.181	2.053
B38	5(19.2)	3(7.9)	0.253	2.778
B40	1(3.8)	0(0)	0.406	2.520
B44	7(26.9)	5(13.2)	0.202	2.432
B49	1(3.8)	6(15.8)	0.225	0.213
B50	1(3.8)	0(0)	0.406	2.520
B51	9(34.6)	13(34.2)	0.973	1.018
B52	2(7.7)	2(5.3)	1.000	1.500
B55	1(3.8)	3(7.9)	0.640	0.467
C02	1(3.8)	0/0	0.406	2.520
C15	1(3.8)	0(0)	0.406	2.520
DQ2	1(3.8)	0(0)	0.406	2.520
DQ4	1(3.8)	0(0)	0.406	2.520

*HLA: human leukocyte antigen; **OR: odd ratio

transplantation for ESRD secondary to VUR between 2005 and 2016, and they were included as the ESRD/VUR group. Thirty-eight healthy donors (14 male, 24 female) were randomly selected as the control group. The single specific primer-polymerase chain reaction method was performed to identify HLA antigens (10). The data comprised age, gender and HLA; A, B, C, DR, and DQ antigens were abstracted from the medical records. The distribution of HLA antigens in both groups was compared. The chi-square test was used for statistical analysis and values of $p<0.05$ were accepted as statistically significant. The relative risk (odds ratio [OR]) was calculated for each HLA tissue antigen type.

Table 3. Distributions of HLA - DRB1 tissue antigens

*HLA TYPE	ESRD/VUR GROUP	CONTROL GROUP		
	n (%)	n (%)	p	**OR
DRB1*01	4(15.4)	0(0)	0.024	2.727
DRB1*03	3(11.5)	6(15.8)	0.728	0.696
DRB1*04	10(38.5)	9(23.7)	0.204	2.014
DRB1*05	1(3.8)	0(0)	0.406	2.520
DRB1*08	1(3.8)	0(0)	0.406	2.520
DRB1*09	1(3.8)	1(2.6)	1.000	1.480
DRB1*10	2(7.7)	2(5.3)	1.000	1.500
DRB1*11	8(30.8)	16(42.1)	0.358	0.611
DRB1*11(5)	1(3.8)	0(0)	0.406	2.520
DRB1*12	3(11.5)	1(2.6)	0.295	4.826
DRB1*13	5(19.2)	9(23.7)	0.672	0.767
DRB1*15	4(15.4)	6(15.8)	1.000	0.970
DRB1*15(2)	1(3.8)	0(0)	0.406	2.520
DRB1*16-A	1(3.8)	0(0)	0.406	2.520
DRB1*16	3(11.5)	0(0)	0.062	2.652

*HLA: human leukocyte antigen; OR: odd ratio

The ratios of the categorical variables among the groups were tested by chi-square analysis. A statistical significance level of alpha was accepted as $p<0.05$. Data analysis was conducted using Statisical Package for Social Sciences (SPSS) software version 15.0 (SPSS Inc.; Chicago, IL, USA).

Results

The mean age of patients in the ESRD/VUR group and control group was 25.2 years (10-41 years) and 43.9 years (20-76 years), respectively (Table 1). The distribution of HLA A, B, DR, and DQ tissue antigens are presented in Tables 2 and 3.

The analysis in terms of HLA A and B distribution revealed no statistical significance between the groups ($p>0.05$). HLA DRB1*01 tissue antigen type had statistical significance between the ESRD/VUR and control groups ($p=0.024$). OR was calculated as 2.727 for HLA DRB1*01. The presence of the HLA DRB1*01 tissue type was associated with a 2.727 increase in odds of ESRD secondary to VUR.

Discussion

The diagnosis and treatment of VUR are important for the prevention of RN and ESRD. The mechanism of familial inheritance in patients with VUR has not yet been well defined in the literature. Nevertheless, HLA tissue antigen subgroups can be used as a guide to other familial diseases, and it could be effective for predicting the

clinical outcomes for VUR. Previous descriptive studies on prognostic markers for VUR focused on genetic factors and HLA tissue antigens (5, 8). HLA class 1 antigens were the first line study groups. Bailey and Walles (7) reported that HLA B12 was high in RN patients. Sengar et al. (11) reported the association between HLA AW32 antigen and urinary anomalies and reflux nephropathy. Torres claimed a possible association between renal failure secondary to RN and HLA B12 in females, HLA B8 and 9 in males, and HLA BW 15 in both genders (8). Our study did not evaluate HLA tissue antigen based on gender distribution, and there were no significant differences between class 1 HLA antigens and ESRD secondary to VUR. This inference can be attributed to the fact that the study was designed with a small group of patients.

The associations between VUR and HLA class 2 antigen were investigated in previous studies. Albarus and colleagues investigated VUR and HLA DQ subgroup associations and found statistical significance (9). Kawauchi et al. (3) reported that HLA DRB1*1101 and 1502 alleles are significantly higher in reflux patients. HLA DRB1*1101 allele levels were low in patients with renal scarring. This finding was explained with inadequate immune response to infectious agents. In contrast to the above finding, we found that HLA DRB1*01 tissue antigen type was higher in patients with ESRD secondary to VUR, and this difference was statistically significant. The presence of HLA DRB1*01 tissue type increases the odds of the risk of ESRD secondary to VUR by 2.727. The HLA DRB1*01 antigen could be interpreted as a poor prognostic factor for the development of ESRD secondary to VUR.

Previous reports reported that the HLA DRB1 allele and its subgroups are associated with familial diseases. The mechanism of antigen action varies according to the binding site and diversity of the synthesized amino acids. The diversity of synthesized amino acids may racially differ even in the same tissue type. The various effects of HLA antigens in Kawauchi et al. (3) and our study can be explained by HLA-DRB1 allele polymorphism, differences in amino acid expression, and racial differences.

Conclusion

This retrospective study assessed only the HLA antigen types and did not investigate other factors affecting the development ESRD secondary to VUR. An association between HLA DRB1*01 tissue antigen and ESRD secondary to VUR was established. The HLA DRB1*01 tissue antigen could be used to predict the treatment and clinical outcomes in RN. This finding should be supported by further studies with larger series.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cerrahpaşa School of Medicine. (Approval Date: 06.09.2016; Approval No: 83045809-604.01.02)

Informed Consent: Informed consent was not taken from patients due to the retrospective nature of the study.

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