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HLA-B*60 and HLA-DR*14 Alleles might be associated with the Hyperuricemic and Possibly Metabolic Syndrome Status in Renal Transplant

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Abstract

Background: Hyperuricemia is frequent among renal transplant recipients. The role of the HLA system in the susceptibility of hyperuricemia is unknown.

Methods: We evaluated the HLA-B and HLA-DRB1 distribution among 160 renal recipients: 132 with hyperuricemia (Group 1) and 28 free of it (Group 2) as well as 381 ethnic-specific Mexican-mestizo population historic controls. The HLA alleles were assessed by PCR-SSP and the HLA allele gene frequencies were obtained by direct gene counting and compared by X^2 test. P values were adjusted by Bonferroni.

Results: The median post-transplant follow-up was 3.9 years. The prevalence of diabetes, hypertension and use of calcineurin inhibitors was similar among groups; however dyslipidemia predominated in Group 1. HLA-B*35 and B*39 alleles were more frequent in Group 2 vs. controls (OR 2.17 95% CI 1.1-4.0; p = 0.01 and OR = 2.17, CI 95% 1.07-4.34; p = 0.04, respectively). Compared to controls, Group 1 had a higher prevalence of the allele HLA-B*60 (OR 3.5 95% CI 1.52-8.3; p = 0.004). The allele HLA-DRB1*14 predominated in Group 2 when compared with Group 1(OR 3.12 95% CI 1.06-9.9, p = 0.03) and controls (OR 2.50 95% CI 1.13-5, p = 0.007).

Conclusion: The HLA allele distribution differed among groups, suggesting that hyperuricemia in the renal transplant setting might be influenced by ethnicity. Prospective studies using predicting HLA models in different ethnic populations are needed.

Keywords

HLA, Hyperuricemia, Renal transplant, Gout

Introduction

In the renal post-transplant setting, the presence of hyperuricemia and gout are frequent problems, with prevalence of 19-84% and 3.5-28%, respectively. Traditionally these conditions have been associated with the use of diuretics, impaired renal function and mainly with the use of cyclosporine A [1-2]. Studies regarding the influence of genetics in gout and hyperuricemia have been primarily limited to familiar uncommon mutations or to genes related to the regulation of renal excretion of uric acid (*SLC22A12, SCL2A9, ABCG2, SLC17A3*, etc.) [3-5]. Only two studies have tested the association of HLA antigens and gout, one of them found no association [6] whereas the other described an increased frequency of HLA-A*28, HLA-B*14, HLA-Cw1, HLA-DRB1*08 and HLA-DQB1*03 in black South African population [7].

On the other hand the coexistence of hyperuricemia with other medical conditions such as diabetes, dislypidemia and hypertension is well known [8]. Further, the association of HLA alleles and certain biochemical traits has recently been described. For instance, in Japanese female individuals, DPB1*03:01 was associated with higher HbA1c and DRB1*14:03 with higher total cholesterol concentration, whereas DPB1*02:01 had a protective effect against high LDL concentration. In males, C*14:02 was associated with abnormal fasting plasma glucose levels [9]. Moreover in Pakistani population, the allele DRB1*13 is more prevalent among diabetic patients [10]. In the same vein, non-alcoholic fatty liver disease has been associated with the presence of HLA-B*65 in Turkish population [11].

Herein we analyzed the association between the HLA-B and

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HLA-DRB1 alleles and the presence of hyperuricemia in renal transplant recipients to determine whether hyperuricemic patients have distinct HLA alleles.

Materials and Methods

Patients

The study was conducted in a tertiary care center. Patients were from a parent study where we studied the incidence of hyperuricemia [12]. Briefly, patients were ≥ 18 years old at the moment of the transplant, had at least one year of post-transplant follow-up, and had a basal serum uric acid (SUA) measurement the day before the transplant and at least three SUA measurements during the post-transplant follow-up. All patients were of Mexican ancestry (at least two generations). Hyperuricemia was defined as at least two elevated SUA determinations of more than 6 mg/dl for women and more than 7 mg/dl for men [12]. In order to be included, HLA haplotype information should also be available. Patients' clinical records were carefully reviewed according to a pre-established protocol. We collected demographic data, comorbidities and drugs use.

The transplant population was classified into two groups: with hyperuricemia (Group 1) and free of hyperuricemia (Group 2). In addition, we used as a control group, the frequencies of ethnic-specific HLA-B/-DRB1 alleles in an admixed Mexican families population (191 families [381 nonrelated individuals]) [13].

HLA typing

Genomic DNA was isolated from peripheral EDTA anti coagulated whole blood employing the Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI, USA). DNA was then precipitated with isopropanol, washed with 70% ethanol and resuspended in sterile distilled water at a final concentration of 0.1-1.0 μg/μL before use.

HLA class I (HLA-B) and HLA class II (HLA-DRB1) were assessed by a PCR-SSP (polymerase chain reaction-sequence specific priming) procedure (InVitrogen HLA-A/B/DR/DQ SSP Unitray®, Carlsbad, California, USA). The PCR products were analyzed by phototyping in 2% agarose gels, stained with ethidium bromide.

Statistical analysis

Gene frequencies of HLA-B, DRB1 and DQB1 were obtained by direct counting. Contingence tables of 2 × 2 were generated and the significance of the differences between groups was determined using Mantel-Haenzel chi-square analysis or Fisher exact test using the EPIINFO statistical program. P values were corrected according to Bonferroni test and considered statistically significant if their value was < 0.05. Odds ratios (OR) with 95 confidence intervals (C.I.) were calculated according to Woolf's method.

Results

We included 160 patients out of 236 patients of the parent study with available HLA data. 132 patients had hyperuricemia (Group 1) and 28 patients were free of it (Group 2). The median post-transplant follow-up was 3.9 years (range 1.2-12.48). The prevalence of hypertension and diabetes was similar among groups (Table 1), whereas dyslipidemia was more prevalent in patients with hyperuricemia. The usual transplant maintenance regimen was based on prednisone, a calcineurin inhibitor (cyclosporine or tacrolimus) and an anti proliferative drug (azathioprine or mycophenolate mofetil (MMF). The use of drugs was similar among groups with the exception of MMF that was less frequently used by Group 2 (Table 1).

Table 1: Clinical characteristics

Variable	Group 1 (n = 132) Hyperuricemia	Group 2 (n = 28) Free of hyperuricemia	P
Age at Transplant	31.2 ± 9.7	35.5 ± 11.9	0.07
Female n, %	55 (40)	11 (39)	0.87
Hypertension n, %	98 (72)	21 (75)	0.75
Diabetes Mellitus n, %	15 (11)	4 (14)	0.51
Dyslipidemia n, %	80 (58)	10 (35)	0.02
Body Mass Index	23.1 ± 4.1	22.4 ± 2.8	0.29
Cyclosplorine A n, %	118 (86)	21 (75)	0.13
Mycophenolate mofetil n, %	58 (42)	2 (7)	0.001
Azathioprine n, %	126 (92)	24 (85)	0.43
Tacrolimus n, %	20 (14)	7 (25)	0.24

HLA-B alleles

Group 2 had a significantly increased frequency of HLA-B*35 (g.f. 0.32) as compared to healthy controls (g.f. 0.16) (OR 2.17 95% CI 1.1-4.0; p = 0.01).

Likewise the frequency of HLA-B*39 was also significantly higher in Group 2 as compared to healthy controls (0.20 vs. 0.10, OR = 2.17, CI 95% 1.07-4.34; p = 0.04), but not when compared to Group 1.

On the other hand, patients with hyperuricemia had a higher prevalence of the allele HLA-B*60 when compared with controls (g.f. 0.04 vs. 0.01, OR 3.5 95% CI 1.52-8.3; p = 0.004).

We did not detect any other significant deviations in the frequency of the remaining HLA-B alleles.

HLA-DRB1 alleles

Regarding the analysis of the HLA-DRB1 loci, the allele HLA-DRB1*14 predominated in Group 2 when compared to Group 1 (g.f. 0.11 vs. 0.04, OR 3.12 95% CI 1.06-9.9, p = 0.03) and controls (g.f. 0.08, OR 2.50 95% CI 1.13-5.0, p = 0.007). We only observed a statistically tendency in the allele DRB1*08 with a higher frequency in Group 2 when compared with healthy control (0.23 vs. 0.12, OR = 1.96, CI 95% 0.99-3.8, p = 0.04).

We did not detect any other significant deviations of the remaining HLA-DRB1 alleles.

Discussion

Herein we evaluated the HLA-B and HLA-DRB1 alleles in a renal transplant population according to the presence of hyperuricemia. Patients free of hyperuricemia presented more frequently the alleles HLA-B*35, B*39 and DRB1*14 whereas the allele HLA-B*60 was more prevalent in the group who developed hyperuricemia.

Hyperuricemia is frequently encountered in renal transplant patients. Its prevalence ranges from 19%-55% in subjects not using cyclosporine A, to 30%-85% in users of this immunosuppressive agent [1-2]. We previously reported incident hyperuricemia in 70% in our own transplant cohort, in which 50% of the cases were detected during the first year after the renal allograft. Further there was no difference in the use of cyclosporine among patients with and without hyperuricemia [3].

Substantial growing epidemiologic and biologic evidence indicates that hyperuricemia is associated with other components of the metabolic syndrome. For instance, increased levels of fibroblast growth factor 21 (FGF219), a regulatory metabolic hormone, have been reported as an independent risk factor for both metabolic syndrome [14] and hyperuricemia [15]. Further some human leukocyte antigen alleles have been associated with biochemical traits such as high HbA1c, high total cholesterol, abnormal fasting plasma glucose and with non-alcoholic fatty liver [9-11]. To our knowledge, only one study has assessed the association of the HLA alleles and hyperuricemia [9]. In this study, Mitsunga and cols evaluating Japanese population, did not find any association with hyperuricemia and six HLA loci (A, B, C, DRB1, DQB1 and DPB1) [9]. Conversely, we found in this selected population, that renal transplant patients free of hyperuricemia presented more frequently the alleles HLA-B*35, HLA-B*39 and HLA-DRB1*14. Conversely, HLA-B*60 was an allele associated with the presence of hyperuricemia.

On the other hand, the HLA has been traditionally considered an ethnicity marker. Further racial differences in the incidence of gout and hyperuricemia have been reported. For instance, the prevalence of gout appears to be higher among African Americans than among

Caucasians [16]. Moreover at the Tokelau population the mean urate concentration ranges between hyperuricemic values [17].

Herein as previously mentioned, we found a higher prevalence of the alleles HLA-B*35, B*39and DRB1*14 in the group free of hyperuricemia. We also found a tendency in DRB1*08, although not statistically significant. This feature was evident even though these alleles are the most prevalent in our population. Both HLA-B*35 and HLA-B*39 are characteristics of Amerindian origin, while DRB1*08 of both Amerindian and mestizo population [18]. Since DRB1*08 is in linkage disequilibrium with HLA-B*35 and HLA-B*39 they are part of a same haplotype, conversely the participation of HLA-DRB1*14 seems to be independent.

We also found a higher prevalence of HLA-B*60 in the hyperuricemic group. As HLA-B*60 is expressed in approximately 10% of Caucasian population, this allele seemed to be incorporated by admixture with Caucasians or White European individuals [19].

Hyperuricemia is the main factor for development of gout. Unlike patients from the general population, gout in renal recipients is more aggressive, with an early onset, with fast tophaceous progression and involves unusual joints [1-2]. Furthermore, hyperuricemia has emerged as a condition that may influence the transplant survival [20]. In this sense, the ability to predict hyperuricemia in these patients is clinically relevant. As the HLA analysis is routinely performed in these patients, the identification of high and low risk alleles could be helpful in the evaluation of susceptibility to hyperuricemia.

We recognize the following limitations of this study. First our sample is relatively small, hampering the strength of our findings. Second it was limited to Mexican mestizo patients and to renal transplant population, restricting its external validity. Third the cross-sectional nature of the study may bias our results. In this sense prospective studies using predicting HLA models in different ethnic populations are needed.

In conclusion we found that certain HLA-B and HLA-DRB1 alleles might protect for the development of hyperuricemia while others are associated with it. Thus, beyond the idea that hyperuricemia in the transplant setting is only secondary to the use of cyclosporine A, it might be also influenced by ethnicity. However further studies in other populations are needed to validate our findings.

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Conflict of Interest

The authors declare none conflict of interest.

Compliance with Ethical Standards

For this type of study formal consent was not required

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