

Human Leukocyte Antigen Alleles and Cytomegalovirus Infection After Renal Transplantation

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Abstract

Background: Several studies have been conducted on the relationship between a number of human leukocyte antigen (HLA) alleles and cytomegalovirus infection (CMV), in kidney transplant recipients, after transplantation. However, only a limited number of HLAs have been investigated, so far, and the results have been contradictory.

Objectives: This study aimed to investigate the relationship between 59 HLA alleles and the CMV infection, in transplant recipients, after kidney transplantation.

Patients and Methods: This retrospective cohort study was conducted on 200 patients, receiving a kidney transplant, in Baqiyatallah Hospital, in Tehran, during 2013. Throughout a one-year follow-up of kidney transplant recipients, in case of detecting the CMV antigen in patients' blood, at any time, they were placed in the group of patients with CMV infection, whereas, if no CMV-specific antigen was developed, over a year, patients were placed in the group of patients without CMV infection, after transplantation. This study investigated the relationship between CMV infection in kidney transplant recipients and 59 HLA alleles, including 14 HLA-A, 28 HLA-B, and 17 HLA-DRB1 cases.

Results: Of all participants, 104 patients (52%) were diagnosed with CMV infection. There was no significant difference between the two groups, with and without CMV infection, in terms of patient's characteristics. The CMV infection, in patients receiving a transplanted organ from deceased donor, was significantly more prevalent than in those receiving kidney transplant from living donor (63% vs. 39%, respectively, $P = 0.001$). Recipients with HLA-B44 were more infected with CMV compared with patients without this allele (80% vs. 50%, respectively, $P = 0.024$); on the contrary, kidney recipients with HLA-DRB1-1 were less infected with CMV than patients without this allele (31% vs. 55%, respectively, $P = 0.020$). There was no significant relationship between CMV infection and other HLA alleles. Results of multivariate logistic regression analysis showed that deceased donor renal transplantation (OR = 3.018, 95%CI: 1.662 - 5.480, $P < 0.001$), presence of HLA-B44 (OR = 4.764, 95%CI: 1.259 - 18.032, $P = 0.022$) and lack of HLA-B8 (OR = 3.246, 95%CI: 1.030 - 10.230, $P = 0.044$) were the independent risk factors for developing CMV infection, after kidney transplantation.

Conclusions: The findings of this study showed that deceased donor renal transplantation and the presence of HLA-B44 can make the kidney recipient susceptible to CMV infection after kidney transplantation; on the other hand, the presence of HLA-B8 can have a protective effect.

Keywords: Cytomegalovirus Infections, Kidney Transplantation, Cytomegalovirus, Kidney Transplantation, Cytomegalovirus, Human Leukocyte Antigen

1. Background

Cytomegalovirus (CMV) is one of the most important infections in kidney transplant recipients. Contact with the virus is determined by the presence of IgG antibody in the plasma, which occurs in more than two-thirds of recipients and donors, before kidney transplantation (1). As a result, generally, at the time of kidney transplantation, organ donors and recipients are positive in terms of exposure to the virus. The CMV can be transmitted from organ donors, via blood or kidney transplant, and concurrent use of immunosuppressant drugs, for the prevention of transplant rejection, may increase the risk of infection and, also, its complications in patients (2, 3). Due to the direct effects of the virus, which is associated

with destruction of infected cells, and due to indirect effects (by stimulating the immune system via mediated cells), the CMV infection can lead to a scenario of chronic fever, leucopenia and invasive organ diseases, such as hepatitis, pneumonitis, pancreatitis, myocarditis, colitis, retinitis, etc. Asymptomatic seropositive individuals are affected with increased risk of long-term complications, after their transplant. Recipients, who are at risk of CMV infection after transplantation, are also susceptible to the long-term complications, including acute or chronic graft rejection, graft vascular sclerosis, increased risk of bacterial and fungal infections, cardiovascular disease, diabetes, malignancy etc. (4).

Various factors have been introduced, as risk factors for CMV infection, such as serologic mismatch, administration of potent immunosuppressant drugs, use of monoclonal or polyclonal antibodies, graft rejection or its treatment, type of graft, and inconsistency of human leukocyte antigens (HLA) (5, 6). Because of HLA genetic diversity, a wide range of diseases, such as ankylosing spondylitis, rheumatoid arthritis, celiac disease, insulin-dependent diabetes, Goodpasture's syndrome etc., are associated with different types of HLA (7-10). On the other hand, several types of HLA have a protective role against the development of a number of diseases, such as skin cancers and Kaposi's sarcoma (11, 12). Although several studies have been conducted on different types of HLA, as one of the risk factors for CMV infection in kidney transplant patients, the results of these studies are contradictory. In other studies, it is suggested that there is no relationship between HLA-A, HLA-B and HLA-DR alleles and the incidence of CMV infection in kidney transplant recipients (13), while in other studies, a number of HLA alleles are introduced as risk factors for CMV infection and more, several of them are even suggested to have a protective role (14-17). In a series of cases, such as HLA-DR7, contradictory results have been reported. For instance, Kraat et al. introduced HLA-DR7 as a risk factor for CMV infection, in kidney transplant patients (18). Nevertheless, Gomez et al. rejected the relationship between CMV and HLA-DR7 (19).

The identification of people at increased risk of developing CMV infection, after transplantation, can help to adopt preventive measures and, consequently, reduce mortality, morbidity and graft rejection.

2. Objectives

Since the results of previous studies on the relationship between HLA alleles and incidence of CMV infection have varied and, as each study only analyzed a few types of HLA, hence, this study aimed to investigate the relationship between 59 HLA alleles and CMV infection, during one year, after renal transplantation.

3. Patients and Methods

This retrospective cohort study was conducted on 200 kidney transplant recipients in Baqiyatallah Hospital, in Tehran, from April 2012 to September 2013. Patients were followed up for one year and were monitored for CMV infection. The diagnosis of CMV infection was based on the presence of CMV-specific antigen in the blood of patients. In case of developing CMV antigen in patients' blood, at any time during the one-year follow up after transplantation, they were placed in the group of CMV infected patients and, if no CMV antigen was developed over the year, patients were placed in the group of patients without CMV infection. All patients were receiving triple therapy regimen of prednisolone, calcineurin inhibitors (CNI), such as cyclosporine and tacrolimus, mycophenolate mofetil or azathioprine. Based on the exclusion crite-

ria, if patients did not refer for follow-up, at the specified times, or did not participate in the tests, they would have been excluded from the study. The study was approved by the Ethics Committee of Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Tehran, Iran.

A check-list was used to collect patients' data, including demographic characteristics (age, sex, height, and weight), underlying diseases, blood group and Rh, characteristics of kidney transplantation (including creatinine level at the time of transplantation, kidney transplant source from a living donor or a deceased donor, history of transplantation, antithymocyte globulin (ATG) therapy and pulse corticosteroid therapy), and 59 HLA alleles, including 14 HLA-A, 28 HLA-B, and 17 HLA-DRB1. Finally, the above characteristics were compared between the two groups of patients, with and without CMV infection and independent prognostic variables for CMV infection were also investigated.

Data analysis was performed using SPSS for Windows 22 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were described by mean and standard deviation and qualitative variables were described by frequency (percentage). Quantitative variables were compared between the two groups of patients, with and without CMV, using independent samples t-test, and qualitative variables were analyzed, using Chi-Square test. The independent prognostic factors for CMV infection, in kidney transplant recipients, were analyzed using multivariate logistic regression analysis. The CMV infection was considered as the dependent variable and variables, which had a $P < 0.1$, in the univariate analysis, were considered as independent variables and were included in the model, using forward conditional method. All $P < 0.05$ were considered as significant.

4. Results

From a total of 200 patients, 108 patients (54%) were male and 92 patients (46%) were female. Range and mean age (SD) of patients were 9 - 76 years and 46 ± 14 years, respectively. The CMV infection was diagnosed in 104 patients (52%) during a one-year follow-up period, after kidney transplantation. There was no significant difference between the two groups with and without CMV, in terms of demographic characteristics, underlying diseases, blood group and Rh (Table 1). There was no significant difference between the two groups in terms of creatinine after transplantation, history of previous transplant, ATG therapy and corticosteroid pulse therapy. However, most of kidney transplant patients with CMV infection received the organ from a deceased donor (63% vs. 39%, $P = 0.001$) (Table 2).

Tables 3 to 5 compare the different alleles of HLA-A, HLA-B and HLA-DRB1 between the two groups. There was no statistically significant relationship between CMV infection and different types of HLA-A ($P > 0.05$). Concerning HLA-B alleles, only kidney transplant recipients with HLA-B44 were significantly more infected with CMV than other patients without this HLA allele ($P = 0.024$) and there was no statistically significant relationship between the CMV in-

fection and other HLA-B alleles ($P > 0.05$). Concerning HLA-DRB1, all kidney transplant recipients with HLA-DRB1-1 were significantly less infected with CMV than patients without this HLA allele ($P = 0.020$). In other words, the presence of HLA-DRB1-1 had a protective effect against CMV infection. There was no statistically significant relationship between CMV infection and other HLA-DRB1 alleles ($P > 0.05$).

In multivariate logistic regression analysis, CMV infection was used as the dependent variable and variables with a $P < 0.1$ (including age, source of graft, HLA-B8, HLA-B44, HLA-B52 and HLA-DRB1-1) in the univariate analysis were entered as independent variables. The analysis was

performed using the forward conditional approach. The results showed that transplantation of kidney, from a deceased donor, compared with those from a living donor, had an OR = 3.018 (95%CI: 1.662 - 5.480, $P < 0.001$) and the presence of HLA-B44 had an OR = 4.764 (95%CI: 1.259 - 8.032, $P = 0.022$) for the development of CMV infection. In addition, the lack of HLA-B8 had an OR=3.246 (95%CI: 1.030 - 10.230, $P = 0.044$) for developing CMV infection. Therefore, the presence of HLA-B8 had a protective effect against the CMV infection. Age, HLA-B52 and HLA-DRB1-1 did not have an independent effect on the risk of CMV infection ($P > 0.05$) (Table 6).

Table 1. Comparison of Demography, Underlying Disease and Blood Groups Between the two Groups With and Without Cytomegalovirus Infection After Renal Transplantation^a

	CMV + (No = 104)	CMV - (No = 96)	P
Age, y	47.8 ± 14.4	43.8 ± 14.1	.050 ^b
Gender			.456 ^c
Male	58 (56)	49 (51)	
Female	45 (44)	47 (49)	
Height, cm	166.0 ± 6.7	166.4 ± 10.5	.698 ^b
Weight, kg	66.8 ± 10.6	65.3 ± 13.4	.377 ^b
Underlying diseases			.335 ^c
Diabetes Mellitus	15 (14)	9 (9)	
Hypertension	41 (40)	40 (429)	
Hypertension and Diabetes Mellitus	19 (18)	10 (11)	
Hypertension and PCKD	4 (4)	3 (3)	
PCKD	3 (3)	2 (2)	
Others	22 (21)	32 (33)	
Blood group			.963 ^c
A	36 (35)	34 (35)	
B	24 (23)	25 (26)	
AB	7 (7)	6 (6)	
O	36 (35)	31 (33)	
Rh			.899 ^c
+	95 (92)	89 (93)	
-	8 (8)	7 (7)	

Abbreviations: CMV, cytomegalovirus; PCKD: polycystic kidney disease.

^aData are presented as mean ± SD or No. (%).

^bIndependent sample t-test.

^cChi square test.

Table 2. Comparison of Kidney Transplant Characteristics Between the two Groups With and Without Cytomegalovirus Infection After Renal Transplantation^a

	CMV + (No = 104)	CMV - (No = 96)	P
Cratinine, mg/dL	1.78 ± 1.27	1.76 ± 1.30	.933 ^b
Transplant source			.001 ^{c,d}
Living donor	36 (35)	57 (59)	
Deceased donor	67 (65)	39 (41)	
Previous transplantation	4 (4)	9 (9)	.117 ^d
ATG therapy	36 (35)	29 (30)	.476 ^d
Corticosteroid pulse therapy	9 (9)	13 (14)	.280 ^d

Abbreviations: CMV, cytomegalovirus; PCKD: polycystic kidney disease.

^aData are presented as mean ± SD or No. (%).

^bIndependent sample t-test.

^cStatistically significant.

^dChi square test.

Table 3. Comparison of Human Leukocyte Antigen-A Alleles Between the two Groups With and Without Cytomegalovirus Infection, After Renal Transplantation

HLA-A	CMV + (No = 104)	CMV - (No = 96)	p ^a
A1	19 (18)	19 (20)	.784
A2	29 (28)	31 (32)	.497
A3	23 (22)	17 (18)	.436
A11	23 (22)	26 (27)	.414
A22	0	1 (1)	.480
A23	4 (4)	4 (4)	1.000
A24	30 (29)	30 (31)	.711
A26	12 (12)	9 (9)	.618
A29	4 (4)	5 (5)	.740
A30	8 (8)	6 (6)	.690
A31	2 (2)	3 (3)	.673
A32	9 (9)	14 (15)	.189
A33	7 (7)	3 (3)	.242
A39	1 (1)	0	1.000
A66	2 (2)	3 (3)	.673
A68	12 (12)	7 (7)	.306
A69	2 (2)	0	.498

Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen.

^aChi square test.**Table 4.** Comparison of Human Leukocyte Antigen-B Alleles Between the two Groups With and Without Cytomegalovirus Infection, After Renal Transplantation

HLA-B	CMV + (No = 104)	CMV - (No = 96)	p ^a
B7	8 (8)	10 (10)	.501
B8	5 (5)	12 (13)	.051
B13	4 (4)	5 (5)	.740
B14	8 (8)	3 (3)	.157
B15	7 (7)	5 (5)	.651
B18	7 (7)	10 (10)	.350
B27	5 (5)	5 (5)	.897
B35	29 (28)	37 (39)	.109
B37	6 (6)	3 (3)	.501
B38	11 (11)	7 (7)	.417
B39	4 (4)	4 (4)	1.000
B40	12 (12)	5 (5)	.109
B41	2 (2)	7 (7)	.091
B42	1 (1)	2 (2)	.609
B44	12 (12)	3 (3)	.024
B47	1 (1)	0	1.000
B48	1 (1)	1 (1)	1.000
B49	10 (10)	8 (8)	.752
B50	12 (12)	6 (6)	.192
B51	27 (26)	20 (21)	.393
B52	8 (8)	16 (17)	.051
B53	2 (2)	0	.498
B55	4 (4)	6 (6)	.436
B56	2 (2)	0	.498
B57	3 (3)	3 (3)	1.000
B58	2 (2)	1 (1)	1.000
B59	0	0	NA
B78	1 (1)	0	1.000

Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen; NA, not available.

^aChi square test

Table 5. Comparison of Human Leukocyte Antigen-DRB1 Alleles Between the two Groups With and Without Cytomegalovirus Infection, After Renal Transplantation

HLA-DRB1	CMV + (No = 104)	CMV - (No = 96)	p ^a
DRB1-1	8 (8)	18 (19)	.020
DRB1-3	18 (17)	21 (22)	.415
DRB1-4	25 (24)	29 (30)	.326
DRB1-7	21 (20)	12 (13)	.143
DRB1-8	4 (4)	2 (2)	.465
DRB1-9	3 (3)	5 (5)	.402
DRB1-10	7 (7)	3 (3)	.242
DRB1-11	38 (37)	33 (34)	.749
DRB1-12	1 (1)	1 (1)	.955
DRB1-13	18 (17)	13 (14)	.462
DRB1-14	15 (14)	8 (8)	.177
DRB1-15	23 (22)	25 (26)	.516
DRB1-16	5 (5)	4 (4)	.827
DRB1-24	0	1 (1)	.297

Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen.

^aChi square test.**Table 6.** Independent Predictive Factors of Post-Kidney Transplant Cytomegalovirus Infection

	B	S.E.	Wald	df	Sig.	Exp (B)	95%CI for EXP(B)	
							Lower	Upper
Deceased donor transplant source	1.105	.304	13.168	1	<.001	3.018	1.662	5.480
HLA B8 -	1.177	.586	4.041	1	.044	3.246	1.030	10.230
HLA B44 +	1.561	.679	5.284	1	.022	4.764	1.259	18.032
Constant	-1.701	.605	7.915	1	.005	.182	NA	NA

Abbreviations: HLA, human leukocyte antigen; NA, not available.

5. Discussion

This study aimed to determine the prevalence of CMV infection in kidney transplant recipients and investigated its association with demographic and clinical factors, especially 59 HLA alleles, including 17 HLA-A, 28 HLA-B and 14 HLA-DRB1. The findings showed that more than half of kidney transplant patients are infected with CMV during one year after transplantation. Multivariate analysis showed that, among the studied factors, deceased donor renal transplantation and the presence of HLA-B44 could increase risk of CMV infection after kidney transplantation, while the presence of HLA-B8 could have a protective effect against the infection.

The CMV infection is the most common complication of solid organ transplantation, which significantly reduces the long-term survival of graft and the organ recipient (17). In line with the results of this study, previous studies also reported that the incidence of active CMV infection, in kidney transplant recipients, ranged around 30% - 56%. The incidence rate is influenced by multiple factors, such as the serologic status of donor

and recipient, in terms of CMV infection, type of graft, type and intensity of immunosuppressive therapy and method of diagnosis of CMV (20). In addition, the use of certain therapeutic agents, such as anti-T-lymphocyte, represents a known risk factor (21). Although several studies have shown that prophylactic treatment significantly reduces CMV infection, following transplantation, there are still numerous controversies about the duration of these treatments (20), which can justify the differences in the results of different studies, about the incidence of CMV infection in transplant recipients.

There are several reports about the risk factors associated with CMV infection (6). The most important risk factors for the incidence of CMV infection, after transplantation, are the incompatibility between donor and recipient, in terms of CMV serological status, and the intensity of immunosuppressive therapy, especially the use of anti-lymphocytes antibody for the induction or treatment of acute rejection, along with the use of usual preventive therapy for transplant recipients (22, 23). It has been suggested that

selection of induced factors by different treatment groups have different effects on the risk of CMV reactivation, after transplantation. In particular, the effects induced by ATG, in several transplant recipients, are associated with a significantly increased risk of CMV infection, while the use of other factors, such as basiliximab, does not have a significant impact on the increase of the risk of CMV infection (24). In our study, a number of patients were under ATG or pulse corticosteroid therapy, which might have a decisive role in the incidence of CMV infection. In addition, as in our study, several of the transplant kidneys were from deceased donor, it was not possible to determine the serologic status of donors and it might have a significant impact on our results. It seems that the differences in the results of studies might be due to the differences in the methods used to assess the disease and also due to the use of different immunosuppressive, antifungal and prophylactic treatments, after the transplantation. In addition, our study showed that deceased donor renal transplantation can independently lead to the increased risk of CMV infection.

Nowadays, it is known that a large number of different diseases are associated with different types of HLA and certain types of HLA have a protective role against the development of certain diseases. Results obtained in the past two decades have shown a relationship between the development of CMV infection and several types of HLA (17). Previously, a number of studies specifically investigated the role of HLAs of kidney transplant recipients in the development of CMV infections, after transplantation. According to Blancho et al. there is no relationship between the alleles of HLA-A, HLA-B and HLA-DR and the incidence of CMV infection. However, HLA-DR7 matching between donor and recipient can increase the risk of CMV infection (13). Kraat et al. reported that kidney transplant recipients, with HLA-DR7, are at greater risk for developing CMV infection (18). However, Gomez et al. rejected this idea (19). Szymczakiewicz-Multanowska et al. stated that CMV infection was observed more frequently in recipients with HLA-A1 than in recipients with HLA-A9 and HLA-DR7 (16). Retiere et al. stated that recipients with HLA-A11, HLA-A32, and HLA-DR11 were more frequently infected with CMV infection, while patients with HLA-A24 or HLA-B7 were less infected (14). The results of Varga et al. study also showed a significant association between HLA-DQ3 and CMV infection, which, was not under the influence of known risk factors such, as induction therapy, rejection, or treatment for rejection (17). Bal et al. suggested that HLA-B51 has a protective role against the development of CMV infection, in recipients of renal transplants (15). The results of our study showed that, among 59 HLA alleles, HLA-B44 increased the risk of CMV infection and HLA-B8 had a protective effect against the infection.

Since HLA alleles are usually tested and investigated, before a kidney transplant, to check the compatibility between the donor and the transplant recipient, it can help clinicians to become aware of the presence of those types of HLA, which make transplant patients

susceptible to the development of CMV infection and, consequently, clinicians could pay more attention to high-risk patients. This finding could be utilized to improve screening guidelines designed for the diagnosis and prophylaxis of transplant recipients.

The present study was a unique research, which investigated the association between 59 HLA alleles and CMV infection, in renal transplants recipients and, to the best of our knowledge, there was no previous study, which had investigated the association on such a large scale. Nevertheless, the study also had several limitations. One of the limitations of this study was its small sample size and it seems that the use of larger sample sizes can be helpful in generalizing the results. Another limitation was the use of various drugs after the transplantation, which might become a confounding factor affecting the incidence of CMV infection in kidney transplant recipients. In addition, we did not examine the laboratory indices, such as creatinine levels, at the time of transplantation, and it might likely be the other confounding factor, which was overlooked in this study.

The results of this study showed that more than half of kidney transplant recipients are infected with CMV infection, within one year after the transplantation. Deceased donor renal transplantation and the presence of HLA-B44 can make the kidney recipient susceptible to CMV infection, while the presence of HLA-B8 can have a protective effect. Since post-transplant infections, especially CMV infections lead to immune suppression in this population, they are among the main causes of complications after transplantation and are a cause for rejection of a transplanted organ, being considered a threat to the survival of organ transplant recipients. Therefore, identifying factors that increase the risk of infections, in this type of patients, can help to recognize high risk and susceptible patients and it can also help therapists to focus more on prevention and better care for patients.

Footnote

Authors' Contribution: Study concept and design: Behzad Einollahi, Eglim Nemati; acquisition of data: Farzaneh Fotuhi, Azadeh Saber; analysis and interpretation of data: Zohre Rostami; drafting of the manuscript: Zohre Rostami, Behzad Einollahi; critical revision of the manuscript for important intellectual content: Behzad Einollahi, Einollahi, Eglim Nemati, Zohre Rostami; statistical analysis: Zohre Rostami; administrative, technical and material support: Azadeh Saber, Farzaneh Fotuhi; study supervision: Behzad Einollahi.

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