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Original Article

The Seroprevalence of Parvovirus B19 among Kidney Transplant Recipients: A Single-center Study

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ABSTRACT. Parvovirus B19 is a DNA virus that is responsible for causing several diseases in humans. Parvovirus B19-induced persistent anemia is one of its manifestations that is relatively common in transplant recipients. This study was aimed to investigate the seroprevalence of parvovirus B19 among kidney transplant recipients. Ninety-one transplant recipients were selected randomly and were investigated for several variables including age, gender, educational status, history of hemodialysis (HD), history of blood transfusion and immunosuppressive therapy. Two milliliters of blood samples were collected via venipuncture and evaluated for anti-Parvovirus B19 IgG antibody using enzyme-linked immunosorbent assay. All recipients were anemic, with 72.5% of them suffering from severe anemia (Hb ≤11 in men and ≤10 in women). Sixty-three patients (69.2%) were seropositive for Parvovirus B19. There was no significant difference in age, sex, educational status, history of blood transfusion, history of HD and immunosuppressive therapy between seropositive and seronegative groups. The seroprevalence of Parvovirus B19 was relatively high in kidney transplant recipients in Urmia, Iran. Our study failed to find a correlation between the severity of anemia and the seropositivity of Parvovirus B19.

Introduction

Anemia is a common problem following renal transplantation. Considering its multifactorial nature, its treatment may be challenging.

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Some proposed causes for post-transplant anemia are acute and chronic blood loss, generalized bone marrow suppression due to immunosuppressants and anti-viral therapy, allograft dysfunction, iron deficiency, hyperparathyroidism, use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and, finally, some viral infections such as Cytomegalovirus or Parvovirus B19.[1-4]

Parvovirus B19 is a non-enveloped icosahedral single-stranded DNA virus that is a member of

the Parvoviridae family.[5] It mostly causes erythema infectiosum in children, also known as "the fifth disease."[6] Many other diseases have been described that are caused by Parvovirus, including hydrops fetalis in fetuses,[7] arthropathies (arthralgias and arthritis) in normal adults[8] and transient aplastic crisis in adults, especially with decreased red blood cell production or increased turnover.[9]

The mode of transmission for Parvovirus B19 in normal hosts is through the respiratory tract. Other possible routes of transmission suggested include donor graft,[1,5,10] transfusion of blood products and viral reactivation due to intense immunosuppression following transplantation.

Renal transplant recipients are susceptible to viral infections because of their immunocompromised background.[11,12] One to 12 percent of adult renal transplant recipients have symptomatic B19 infection during the first year after transplantation.[10,13,14] The immunocompromised state may prevent an effective antiviral immune response, which can potentially lead to persistent viremia and chronic anemia that is resistant to erythropoietin.[4]

Many immunocompetent individuals with detectable B19-specific IgG were completely asymptomatic or had non-specific symptoms of an upper respiratory tract illness.[4] Given the suppressed immune system in transplant recipients, most of them may lack the clinical symptoms of acute B19 infection.

Although there are evidences supporting the high frequency of past Parvovirus B19 infection among healthy adults (60–85% according to serologic findings),[15-17] there is a paucity of data regarding the serologic prevalence of Parvovirus B19 in the transplant recipient population.

This study was aimed to investigate the seroprevalence of Parvovirus B19 among kidney graft recipients at the Imam Khomeini Hospital of Urmia in North-Western Iran.

Materials and Methods

This cross-sectional descriptive study was conducted with the approval of the Scientific and Ethical Review Board of Urmia University of Medical Sciences (UMSU), Urmia, Iran.

One hundred adult kidney transplant recipients aged 15 years and above, who had undergone their first kidney transplantation from living or deceased donor at the Imam Khomeini Training Hospital of Urmia, Iran, were included in this study. One of every five recipients who were referred to the Department of Transplantation in a three-month-period was selected randomly. Patients with multi-organ transplantation or second kidney transplantation, and also those not willing to participate, were excluded from the study (nine subjects refused to participate in the study). Finally, 91 recipients were enrolled in the study.

An informed consent was obtained from each patient prior to participation in the study. Two milliliters of blood was obtained via venipuncture for the serological study. Samples were centrifuged and serum was separated without delay. The sera were then stored at -20°C and tested for anti-Parvovirus B19 IgG by enzyme-linked immunosorbent assay (ELISA; Diapro, Italy). The presence of anti-Parvovirus B19 IgG antibody was considered as evidence of prior exposure to the parvovirus.

The hemoglobin (Hb) and mean corpuscular volume (MCV) levels were measured on the cell counter (Sysmex K-1000, TOA Medical Electronics Co. Ltd., Kobe, Japan).

Anemia was defined according to the American Society of Transplantation as Hb <130 g/L for adult males or <120 g/L for adult females. Anemic patients were divided into three sub-categories according to severity: (a) mild for males, Hb 120–130 g/L, and females, Hb 110–120 g/L; (b) moderate for males, Hb 110–120 g/L, and females, Hb 100–110 g/L; and (c) severe for males, Hb <110 g/L, and females, Hb <100 g/L.[18]

All patients were tested additionally for hepatitis B surface antigen (HBsAg) (Diasorin, USA), anti-hepatitis C virus (HCV) antibody (Diasorin, USA) and anti-human immunodeficiency virus (HIV) (Biotest, Germany) using the ELISA method.

Data were collected regarding the following variables: Age, gender, educational status, ma-

rital status, etiology of end-stage renal disease (ESRD), duration of ESRD, history of hemodialysis (HD), history of blood transfusion and immunosuppressive therapy.

All collected data were analyzed using SPSS software version 16 (Chicago, IL, USA). Descriptive statistics were reported as mean ± SD for continuous variables and as frequency (%) for dichotomous variables. To evaluate the relationship between the different factors, we performed the Chi-square analysis. Quantitative variables were compared using an Independent t-test. *P*-values lower than 0.05 were considered statistically significant.

Results

Ninety-one renal transplant recipients were selected randomly among recipients who underwent kidney transplantation at the Imam-Khomeini Hospital of Urmia, and they were enrolled in the study after signing an informed consent for blood sampling and laboratory assays.

Mean age of the patients was 35.4 ± 14.5 years (six to 65 years old) and there were 61 males (67%) and 30 females (33%). Fifty-nine patients (64.8%) were married and 32 patients (35.2%) were single.

Nineteen patients (20.9%) were illiterate, 20 patients (22%) had studied until elementary school, ten patients (11%) until the guidance school, ten other patients (11%) up to high school, 31 patients (34%) had a diploma and one patient (1.1%) had an academic degree.

The etiology of renal failure among the study patients included glomerulonephritis in 33 cases (36.2%), hypertension (HTN) in 28 cases (30.8%), polycystic kidney disease (PCKD) in 12 cases (13.2%), nephrolithiasis and focal and segmental glomerulosclerosis (FSGS) in two cases each and diabetes mellitus (DM), Alport's syndrome, neurogenic bladder and urinary infection in one case each (1.1%).

Sixty-five patients (71.4%) underwent HD prior to renal transplantation, while 26 patients (28.6%) had no such history. Only 37 patients (40.7%) had a history of blood transfusion. The mean duration post-transplantation of the participants at the time of the study was 5.47 ± 5.19 years.

The mean anti-Parvovirus B19 IgG titer among the study patients was 58.2 ± 64.8. IgG titer less than 4 was considered as negative, 4–5.5 was in the borderline range and more than 5.5 was considered as positive for anti-Parvovirus B19. Thus, 63 patients (69.2%) were seropositive for Parvovirus B19, 22 patients (24.2%) were seronegative and six patients (6.6%) had an IgG titer in the borderline range. For performing the analysis, we included the borderline cases with the seronegative ones. With this, the seronegative group consisted of 28 cases (30.8%). The mean anti-Parvovirus B19 IgG titer in the seropositive group was 83.0 ± 63.7, and 2.38 ± 1.51 in the seronegative group ($P = 0.000$).

Some important patient characteristics including age, gender, educational level, history of HD and history of blood transfusions were compared among the seropositive and seronegative groups (Table 1). As demonstrated in the table, there was no significant difference in the age ($P = 0.83$), gender ($P = 0.52$), educational status ($P = 0.57$), history of blood transfusion ($P = 0.85$) and history of HD ($P = 0.61$) between the two groups.

The mean serum Hb level in the study population was 10.45 ± 0.93 mg/dL; it was 10.43 ± 0.87 mg/dL in the seropositive group and 10.48 ± 1.08 mg/dL in the seronegative group. There was no significant difference between the two groups ($P = 0.19$).

According to the criteria for anemia in the guidelines of the American Society of Transplantation, all the cases (100%) were anemic, and 66 recipients (72.5%) had severe anemia.

Among patients with severe and moderate anemia, 47 (71.2%) and 16 patients (64%), respectively, were seropositive for anti-Parvovirus antibody, and there was no significant difference between the two groups ($P = 0.506$). Also, 47 patients in the seropositive (74.6%) and 19 patients (67.9%) in the seronegative group had severe anemia; again, there was no significant correlation between Parvovirus seropositivity and severity of anemia ($P = 0.506$). Nine patients (9.9%) had renal dys-

Table 1. Patient characteristics in the two different groups with positive or negative anti-Parvovirus B19 IgG.

Characteristics	Anti-PB19 positive (N = 63)	Anti-PB19 negative (N = 28)	*P*-value
Age	35.5 ± 14.4	35.2 ± 14.9	0.83
Gender			
Male	41 (65.1%)	20 (71.4%)	0.52
Female	22 (34.9%)	8 (28.6%)	
Education			
Illiterate	15 (23.8%)	4 (14.3%)	
Lower than diploma	27 (42.9%)	13 (46.4%)	0.57
Diploma and higher	21 (33.3%)	11 (39.3%)	
History of blood transfusion			
Positive	26 (41.3%)	11 (39.3%)	0.85
Negative	37 (58.7%)	17 (60.7%)	
History of hemodialysis			
Positive	44 (69.8%)	21 (75.0%)	0.61
Negative	19 (30.2%)	7 (25.0%)	
Anti-B19 IgG titer	83.0 ± 63.7	2.38 ± 1.51	0.00
Hemoglobin (mg/dL)	10.43 ± 0.87	10.48 ± 1.08	0.19
Anemia			
Severe	47 (74.6%)	19 (67.9%)	0.50
Moderate	16 (25.4%)	9 (32.1%)	

function, defined as serum creatinine ≥1.5 mg/dL for men and ≥1.3 mg/dL for women. Even when impaired renal function was taken into consideration, there was no statistically significant association between Parvovirus seropositivity and severity of anemia.

In our study, we found severe anemia in 90% of the patients who received azathioprine as against only 63.9% of patient who had not received this drug. Thus, a significant correlation was found between the administration of azathioprine as an immunosuppressive treatment and the severity of anemia (P = 0.007). On the other hand, 39 patients (63.9%) who received mycophenolate mofetil (MMF) and 27 patients who were not treated with MMF also had severe anemia. The difference was statistically significant; the group that was not treated with MMF was shown to have more severe anemia (P = 0.007).

Discussion

Infection with Parvovirus B19 presents with several clinical manifestations. The most common manifestations of B19 infection in immunosuppressed patients are pure red cell aplasia and other cytopenias.[4,9,19] Thus, this diagnosis should be considered in transplant recipients with unexplained anemia and reticulocytopenia or pancytopenia.[19]

Chronic anemia is a common problem after renal transplantation,[3] and affects more than 40% of recipients. In our study, all the cases had anemia according to the criteria of the American Society of Transplantation.

The available reports have mentioned the prevalence of patients with severe anemia (defined as Hb ≤11 and ≤10, respectively, in male and female patients) to be almost 10%.[20] Nevertheless, in our population, 72.5% of the recipients had severe anemia. This higher prevalence of severe anemia, and particularly its more severe involvement, may be attributed to the bad nutritional habits in the region of west-Azerbaijan, or poor compliance of patients in following treatment with hematinics.

Anemia has been reported in almost 40% of the general Iranian population.[21] Iron deficiency has been reported to exist in a major part of the people with anemia (57% in a population of Iranian healthy girls).[22] Extra-

polating this data, it could be expected that a major part of the anemic recipients in our study may be having pre-existing iron deficiency and nutritional problems.

In this study, 69.2% of the patients were serologically positive for anti-Parvovirus B19 antibody. We did not evaluate the anti-Parvovirus IgM antibody; hence, investigating the presence of acute infection in this study was not possible. The prevalence may seem to be higher than expected. Reviewing some reports on the seroprevalence of the Parvovirus B19 in the healthy adult population may help in changing our opinion in this regard. It has been reported that more than 70% of the adults show serologic evidence of past Parvovirus B19 infection.[15-17] However, in the study of Mahmudi et al on 730 Iranian healthy blood donors, 46% were positive for anti-B19 IgG.[23]

Three of eight (38%) erythropoietin-resistant severely anemic transplant recipients were demonstrated by Egbuna et al to be positive for B19 by polymerase chain reaction (PCR).[20] Cavallo et al reported a higher Parvovirus B19 infection, detected by PCR, in transplant recipients with anemia compared with recipients without anemia (23% compared with 5%).[24] In our study, there was no statistically significant relationship between the severity of anemia and positivity of Parvovirus B19 using the ELISA method.

Available evidence has emphasized that in organ transplant recipients, diagnosis by serology can be confounded by the administration of blood products or immunoglobulin after transplantation, because these therapies may result in false-positive IgG antibody tests.[4]

In a study by Soliman et al in Egypt, the sensitivity, specificity and accuracy of anti-Parvoviral IgG was indicated to be 81.2%, 53.4% and 61%, respectively, in a sample population of pediatric oncology patients. They concluded that in oncology patients (who exhibited weak immune response, like transplant recipients), screening with PCR rather than serology is more likely recommended.[25] Although the preferred diagnostic modality for the detection of Parvovirus B19 is identification of the viral DNA by PCR, in this study the ELISA method was used for detecting IgG antibodies toward viral capsid proteins to determine previous exposure and infection of the patient.

As demonstrated above, there was no significant difference in age, gender, educational status, history of blood transfusion and history of HD between the seropositive and seronegative groups.

Several studies have suggested that post-transplantation anemia may correlate with several factors, including iron deficiency, chronic inflammation, hyperparathyroidism and treatment with ACEI/ ARBs or anti-viral therapy. Unfortunately, in this study, we did not evaluate any of the mentioned factors, which can have confounding effects on the results of our study.

Azathioprine is a major immunosuppressant used to prevent rejection after transplantation. Bone marrow suppression is an adverse effect of this agent, presenting with leukopenia, thrombocytopenia and anemia.[26] This study found a significant correlation between the administration of azathioprine as an immunosuppressive agent and the severity of anemia (P = 0.007).

The seroprevalence of Parvovirus B19 was relatively high in kidney transplant recipients in Urmia, Iran. Our study failed to find a correlation between the severity of anemia and the seropositivity of Parvovirus B19.

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