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The Seropositivity of Parvovirus B19 among Kidney Transplant Recipients

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Abstract

Background Parvovirus B19 (PV-B19) is a single strand DNA virus that is responsible for causing several diseases in humans. Parvovirus B19 induced persistent anemia or/and pancytopenia or/and reticulocyteopenia in renal transplant recipients (RTRs).

Objective To find out any association between PV-B19 reactivation / primary infections with abnormal renal function tests, and post-transplantation period in renal transplant patients.

Methods A quality enzyme linked immunosorbent assay technique was applied for detection of anti-human PV-B19 IgM (DRG-Germany) and IgG (DRG- Germany) in sera of 50 renal transplant recipients followed up for three successive months and 50 normal were collected from the Center of Kidney Diseases and Transplantation in the Medical City of Baghdad and Al-Khayal Hospital and other many private laboratories, Iraq, during the period from August 2015 till February 2016. The age was ranged from 11-57 years.

Results This prospective study included fifty renal transplant recipients with fifty subjects as a control group. The mean ± standard deviation of ages for RTRs was 32.90 ±12.76, which was comparable to that of healthy controls mean 34.02 ± 14.23 ranging for both RTRs and control group between 11-57 years old. Thirty five (70%) RTR aged less than 40 years, and the remaining fifteen (30%) were above 40 years old, and 38/50 (76%) of these RTRs were males. Seropositivity rate in control was 2/50 (4%) but seropositivity rate in patients was 10% (5 cases) and 10% (5 cases) as turning positive for an individual occurrence of human PV-B19 IgM alone at P value = 0.0299 and 9/50 (18%) from control positive for IgG, while 60% (30 cases) for a similar individual rate of positive human parvovirus B19 IgG at P value < 0.0001.

Conclusion The human PV-B19 infection rate was significantly higher among renal transplant recipients than normal controls. Infections correlated with abnormal renal functions tests, and which may in turn cause anemia and/or reticulocytopenia.

Keywords Parvovirus-B19, anemia, reticulocytopenia, renal transplant recipients, ELISA

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List of abbreviation: CKD = Chronic kidney disease, ESRD = End-stage renal disease, PV-B19 = Parvovirus B19, RTRs = Renal transplant recipients

Introduction

Renal transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). In Iraq, few studies were recently conducted on detecting viral infections or reactivations in Iraqi renal transplant recipients (RTRs) [1,2].

One of the viruses that have been shown to have a role in morbidity and mortality in RTR and post-transplantation immune suppression is Parvovirus B19 (PV-B19). PV-B19 is a

common human pathogen, causing erythema infectiosum in children, transient aplastic crisis in patients with chronic hemolytic anemia or hydrops fetalis and abortion in pregnant women. Immunosuppressed patients can fail to mount an effective immune response to PV-B19, resulting in prolonged or persistent viremia [3].

RTRs can develop symptomatic PV-B19 infections as a result of primary infection acquired via the usual respiratory route or via the transplanted organ, or because of reactivation of latent or persistent viral infection [4]. The most common manifestations of PV-B19 infection in immunosuppressed patients are pure red cell aplasia, reticulocytopenia, and erythropoietin-resistant severe anemia (hemoglobin (Hb) less than 11 mg/dl in male and 10 mg/dl in female) and other cytopenias. PV-B19 infects and lysis proerythroblasts, preventing maturation of the erythroid cells causing anemia. This can be detected by testing bone marrow biopsies where giant proeythroblasts with intranucleareosinophilic inclusion body like nucleoli can be seen as diagnostic markers of PV-B19 infection [4,5].

In addition, as a recent discovery and an interesting finding, most frequently detected virus in RTRs is PV-B19 [6]. It is noteworthy to mention that among viruses, only the intrarenal persistence of B19 DNA and PV-B19 viremia was directly associated with the development of chronic allograft injury, whereas human cytomegalovirus or Epstein-Barr Virus DNAemia is a risk factor for acute rejection [6,7].

Regarding the diagnosis of PV-B19, it should be considered in transplant recipients with unexplained anemia, erythropoietin-resistant severe anemia and reticulocytopenia, pancytopenia, acute or chronic kidney dysfunction or post-transplantation rejection, collapsing glomerulopathy, and thrombotic microangiopathy [7]. Prompt diagnosis of PV-B19 infection in RTR requires a high index of suspicion and careful selection of diagnostic tests, which include serology and polymerase chain reaction [8]. Most patients benefit from intravenous immunoglobulin therapy IgG and/or alteration or reduction of immunosuppressive therapy. The neutralizing antibodies are able to clear the infection usually by 5^{th} to 10^{th} day of infection. It is proposed that with the rising titers of IgG the virus is cleared and the giant proerythroblasts are replaced by regenerating erythroid cells [9].

Moreover, most patients after therapy remain normal until seven months later; thus, IgG therapy of PV-B19 is highly curable and reliable. The only weak point is that anemia and other clinical manifestations caused by PV-B19 are underestimated and mostly overlooked by clinicians. Early recognition of the virus and prompt treatment spares the patient unnecessary exposure to blood transfusions, erythropoietin and renal disease caused by the virus.

However, to the best of our knowledge, there is no previous study on PV-B19 in RTRs in Iraq, therefore, this study aimed to prospectively investigate the sero-prevelance of PV-B19 in Iraqi RTRs.

Methods

This prospective descriptive study was conducted with the approval of the Scientific and Ethical Review Board of Al-Nahrain University/ College of Medicine.

Fifty kidney transplant recipients that's included 38 males and 12 females, who had undergone their first or second kidney transplantation from living donor at from the Center of Kidney Diseases and Transplantation in the Medical City of Baghdad and Al-Khayal Hospital, were included in this study followed for three successive months to detection of viral load. The blood samples collected during the period from August 2015 till February 2016. An informed consent was obtained from each patient prior to participation in the study. Three milliliters of blood were obtained via venipuncture for the serological methods. These three milliliters of samples were

centrifuged by gel tube and serum were separated without delay. The sera were stored at -20 °C and tested for anti-Parvovirus B19 IgG and IgM by enzyme linked immunosorbent assay (ELISA; DRG/ Germany). The Hb and mean corpuscular volume (MCV) levels were measured on the cell counter (Sysmex K-1000, TOA Medical Electronics Co. Ltd., Kobe, Japan).

Results

In this study, 27/50 patients were anemic (hemolytic anemia and 23/50 patients were non-anemic). The mean serum creatinine value for patients was 1.66±1.17 ranging between 0.54 and 7.10 mg/dl, but in normal population was 0.81±0.118. Sixteen out of fifty (32%) of the patients had impaired renal function; (serum creatinine value more than 1.2 mg/dl). The mean for glomerular filtration rate (GFR) that estimated by the Modification of Diet in Renal Disease study equation GFR (MDRD); its value was 67.69±30.38 ranging between 12.75 to 150.9 ml/min/1.73 m^2. The GFR (that calculated by MDRD equation) classified into four groups according to the risk of it, high risky group (GFR <30), moderate risk group (GFR 30-60), low risk group (GFR 61-90), and normal or no risk group (GFR >90). But in normal population, the mean of GFR ±SD was 110.5±10.8.

In this study, the results showed non-significant association between seropositivity of PV-B19 and serum creatinine (P=0.99, 0.364) for IgG and IgM respectively. Also, the results of IgG for human PV-B19 showed non-significant differences with post transplantation period, while the positive IgM for human Parvovirus B19 showed significant differences with infection in the first six months after transplantation because the patients highly immunosuppressant.

The results of this study for IgG showed non-significant association low level of Hb (anemia) for RTR (P=0.77), (Table 1) while PV-B19 IgM showed significant differences in regard to anemic group (0.021), (Table 2).

Table 1. Association between anemic status and human Parvovirus B19 IgG

IgG	Negative		Positive		Turing positive		Total	
	Count	%	Count	%	Count	%	Count	%
*Anemic	10/50	20	17/50	34	0/50	0	27/50	54
Not Anemic	10/50	20	13/50	26	0/50	0	23/50	46
Total	20/50	40	30/50	60	0 /50	0	50/50	100
P value = 0.773								

*Anemic: Hb less than 11 mg/dl in male and 10 mg/dl in female

Table 2. Association between anemic status and human Parvovirus B19 IgM

IgM	Negative		Positive		Turing positive		Total	
	Count	%	Count	%	Count	%	Count	%
*Anemic	23/50	46	0/50	0	4/50	8	27/50	54
Not Anemic	17/50	34	5/50	10	1/50	2	23/50	46
Total	40/50	80	5/50	10	5/50	10	50/50	100
P value = 0.021								

*Anemic: Hb less than 11 mg/dl in male and 10 mg/dl in female

Discussion

The use of more aggressive immunosuppressive regimens for preventing/reducing rates of acute kidney rejection in RTRs, has adversely led to emergence of viral infections as an important cause of allograft loss [10]. Parvovirus B19 is one of these emerging viral infections after transplantation; PV-B19 causes several different clinical diseases and serious complications especially in renal transplant recipients [11].

Infection with human PV-B19 presents with several clinical manifestations. The most common manifestations of PV-B19 infection in immunosuppressed patients are anemia and other cytopenias [12]. Thus, this diagnosis should be considered in transplant recipients with unexplained anemia and reticulocytopenia or pancytopenia. Anemia is a common problem after renal transplantation and affects more than 40% of recipients [13]. In this study, 54% cases had anemia according to the criteria of the American Society of Transplantation (Hb ≤11 mg/dl in male and ≤10 mg/dl in female). The available reports have mentioned the prevalence of patients with severe anemia (defined as Hb ≤11 and ≤10, respectively, in male and female patients) [14].

Seropositivity of human PV-B19 in renal transplant recipients includes:

A) IgG serostatus: The true incidence of PV-B19 infection in renal transplant patients may be underestimated, because PV-B19 serology may not be routinely searched in transplanted patients. Moreover, serological tests may fail to detect PV-B19 infection in immunosuppressed patients [11].

Furthermore, easy and rapid mode of spread through respiratory route may play an important role in the increased prevalence of this virus in our community [15].

In the control group of this study, the seroprevalence of PV-B19 IgG was 18%; these IgG-positive healthy persons might be at the end of resolving their B19 viremia or that some of these controls may had very-low-titer PV-B19 DNA that persisted for longer than predicted by the standard natural history model [16]. On the other hand, in this study, the rate of PV-B19 IgG was 60% in RTRs. Compared to control group, this ratio was too high, because all of the patients involved in this study were a high-risk population, namely immunocompromised.

In a study by Khameneh et al in Iran, the seroprevalence of PV-B19 IgG was 69.2% of renal transplant recipients [14]. In a study by Soliman et al in Egypt, the sensitivity, specificity and accuracy of anti PV-B19 IgG in a sample population of pediatric oncology patients were indicated to be 81.2%, 53.4% and 61%, respectively. This was explained that cancer patients exhibited weak immune response, like transplant recipients [17].

B) IgM serostatus: Total prevalence of IgM antibodies to human PV-B19 in control group was 4% (2 samples were positive out of total 50 tested), but during follow-up of RTR, 10% were IgM-positive, 10% were IgM-Turing positive and 80% were IgM-Negative of PV-B19 at P value = 0.02.

This seropositivity of PV-B19 IgM refers to acute infection. It is known that the PV-B19 infection is either due to reactivation of a latent infection in a general immunosuppression situation (18) or it is the result of a prolonged primary infection in an immunocompromised individual [19,20].

These findings are attributed mainly to reduced RTR immunity by the use of immunosuppressive regimen leading to human PV-B19 reactivation and rapid replication causing the infection in patients. And as a response to infection, the remaining immune system in RTRs secretes antibodies type IgM in an attempt to combat or curb the infection of human PV-B19. According to the results of the current study, estimating serum level of anti PV-B19 IgM in RTR sounds a good test reflecting first, the immune suppression status of RTR and second evaluating the presence of emerged viral infection of PV-B19.

Both PV-B19 IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days [14,21]. Because IgG antibody may persist for years, diagnosis of acute infection is made mainly by the detection of IgM antibodies.

This study concluded that the seroprevalence of PV-B19 was relatively high in kidney transplant recipients in Iraq. The incidence of PV-B19 infection might be underestimated in the renal transplant population. Patients are not routinely tested for this virus because the diagnosis is not often considered and because selection of diagnostic tests can be confusing.

Blood film and reticulocyte counting should be recommended as a routine screening programmatic least every two months, and PV-B19 viral load measurement is recommended for those who had reticulocytopenia. This study recommends Iraqi transplant centers to include serological tests for the detection of PV-B19 infection in kidney donors and recipients.

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Author contributions:

Hlail: Sample collection, serology and hematology working and manuscript writing. Dr. Abdulamir: study design, statistics, and final revision of manuscript. Dr. Al-Saedi: Consultant nephrologist helped in selection of patients.

Conflict of interest

The authors have no conflicts of interest.

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