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Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd

Infectious disease research doi: 10.1016/S2222-1808(16)61078-2

Serological markers of Epstein-Barr virus in renal transplant recipients

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ARTICLE INFO

Article history:
Received 22 Mar 2016
Received in revised form 1 Apr, 2nd revised form 14 Apr, 3rd revised form 26 Apr 2016
Accepted 20 May 2016
Available online 9 Jun 2016

Keywords:
Epstein-Barr virus
Renal transplantation
Serology
Sudan

ABSTRACT

Objective: To detect serological markers [immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies] of Epstein-Barr virus in renal transplant recipients in Sudan.
Methods: A cross sectional study was designed to detect serological markers of Epstein-Barr virus from 152 renal transplant recipients using ELISA.
Results: The results showed that the percentage of renal transplant patients was increased with age, 71.05% of the patients were males, and 56.57% were liveing in cities. The most transplant patients were employee (28.95%) and were housewife (26.32%). The numbers of renal transplant patients were increased every year, and 85.53% of the patients had transplantation in Sudan and 14.47% of patients had transplantation in other countries. Diseases associated with renal transplant patient were hypertension 18.42%, infectious diseases 7.24%, renal diseases 3.95%, atrophy 6.58%, gout 2.63% and other diseases 61.18%. Serological test indicated that among the 152 renal transplants recipient 143 (94%) were IgG positive indicating past infection, while 4 (3%) were IgM positive indicating active infection. Most IgG positive patients have hypertension and atrophy diseases, whereas, IgM positive patient have atrophy disease. IgM positive cases were administrated 75% prograf and 25% cyclosporine as an immunosuppressive drug. While IgG positive cases were administrated 83.92% prograf, 13.29% cyclosporine, and 2.79% prograf plus prednisolone as an immunosuppressive drug.
Conclusions: Finally we concluded that most Sudanese renal transplants recipient studied were previously infected with Epstein-Barr virus, while few of them were recently infected.

1. Introduction

The advent of solid organ transplantation for the treatment of patients with end-stage organ failure has been one of the most exciting medical advances in the late 20th and early 21st centuries[1]. However, complications such as infection and allograft rejection were remaining major causes of morbidity and mortality. Epidemiologically, some viral infections are the result of community exposures (influenza, adenovirus), whereas some are commonly transmitted with the allograft (cytomegalovirus, Epstein-Barr virus), and others are the result of more distant exposures reactivated in the setting of immune suppression (chicken pox and varicella zoster as shingles)[2,3].

Epstein-Barr virus, also called human herpesvirus 4, belongs to subfamily Gamma herpesviridae, genus *Lymphocryptovirus*, species human herpesvirus, affecting more than 90% of the adult population. Epstein-Barr virus is associated with a number of malignant lymphomas, including Burkitt lymphomas, Hodgkin lymphomas, immunodeficiency-associated lymphoproliferative disorders, and subset of diffuse large B-cell lymphomas[4]. Epstein-Barr virus targets B-lymphocytes and achieves latent infection in a circular episomal form. Different latency patterns are recognized based on latent gene expression pattern[5].

In early childhood Epstein-Barr virus infection is asymptomatic, while late primary infection is manifested through the symptoms

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The journal implements double-blind peer review practiced by specially invited international editorial board members.

of infectious mononucleosis[2]. The majority of symptomatic infections in renal transplant recipients are primary infection, related to reactivation of donor virus[6,7].

Epstein-Barr virus-associated lymphoproliferative diseases expressed all Epstein-Barr virus latent antigens (type III latency) in immunodeficient patients and limited antigens (type I and II latencies) in immunocompetent patients. Post-transplantation lymphoproliferative disease is the prototype exhibiting type III Epstein-Barr virus latency[8]. The majority of post-transplantation lymphoproliferative disease cases after solid organ allografting are derived from B-cell lineage, which may or may not be Epstein-Barr virus-positive. A minority of cases are derived from T-cell lineage and is typically Epstein-Barr virus-negative[8].

The risk of post-transplantation lymphoproliferative disease development can be altered by the type of immunosuppression, with higher incidence rates observed in patients receiving cytolytic therapies, including antithymocyte globulin and OKT3[9]. Fludarabine, azathioprine, and other agents causing profound T-cell suppression or mutagenicity are also implicated in pathogenesis of post-transplantation lymphoproliferative disease[10,11]. To avoid kidney donation from seropositive donor to seronegative recipient both recipient and donor candidate should be routinely tested for Epstein-Barr virus immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies before transplantation[12]. The aim of the present study was to detect serological markers (IgG and IgM antibodies) of Epstein-Barr virus in renal transplant recipients in Sudan.

2. Materials and methods

A cross sectional study was designed to estimate the prevalence of Epstein-Barr virus seropositive recipients in Sudanese population. Study was ethically approved by the committee of the Faculty of Medical Laboratory Sciences, University of Khartoum. Informed consent was obtained from 152 participants in Ahmed Gasim Hospital and Soba University Hospital in Khartoum State, Sudan from May to August 2015. Demographic and clinical data include age, gender, residence, occupation, date of transplantation, place of transplantation, disease history and drugs used were collected using questionnaire. Blood samples were collected from participants during routine follow up and Epstein-Barr virus antibodies (IgG and IgM to viral capsid antigen) were detected by EUROIMMUN indirect ELISA kits using Tecan analyzers, and data were presented as percentage.

3. Results

The results showed that the percentage of renal transplant patients was increased with increasing age, 71.05% of the patients were males, and most of them (56.57%) were living in cities. The occupation of the transplant patients was 26.32% housewife, 28.95% employee, 19.74% students, 19.74% tradesman and 5.29% farmers. The number of transplant patients was increased each year, and 85.53% of the patients had transplantation in Sudan and 14.47% of patients had transplantation to other countries. Diseases associated with renal transplant patient were hypertension (18.42%), infectious diseases (7.24%), renal diseases (3.95%), atrophy (6.58%), gout (2.63%) and other diseases (61.18%) (Table 1). Among the 152 renal transplant recipients 143 (94%) were IgG positive indicating past infection and 9 (6%) were negative. While 4 (3%) of renal transplant recipients were IgM positive indicating active infection (Figure 1).

Table 1
Basic characteristic for renal transplant patients. *n* (%).

Characteristics		Number of patients
Age	1–20	10 (6.58)
	21–30	34 (22.37)
	31–40	50 (32.89)
	More than 40	58 (38.16)
Gender	Male	108 (71.05)
	Female	44 (28.95)
Residence	Rural	66 (43.43)
	Urban	86 (56.57)
Occupation	Housewife	40 (26.32)
	Employee	44 (28.95)
	Student	30 (19.74)
	Farmer	8 (5.26)
	Tradesman	30 (19.74)
Date of transplantation	1998–2005	17 (11.18)
	2006–2009	26 (17.11)
	2010–2013	60 (39.47)
	2014–2015	49 (32.23)
Place of transplantation	Sudan	130 (85.53)
	Other countries	22 (14.47)
Disease	Hypertension	28 (18.42)
	Infection	11 (7.24)
	Renal disease	6 (3.95)
	Atrophy	10 (6.58)
	Gout	4 (2.63)
	Others	93 (61.18)
Drugs use	Prograf	126 (82.89)
	Cyclosporine	19 (12.50)
	Prograf + prednisolone	7 (4.61)

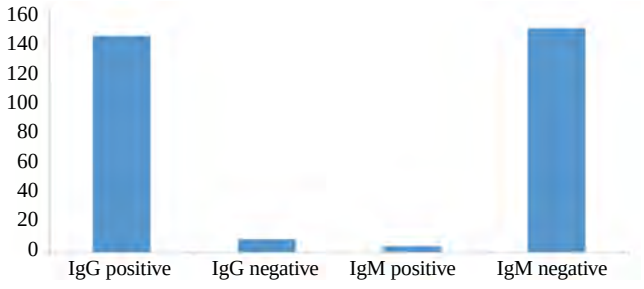

Figure 1. Serology test for Epstein-Barr virus in the renal transplant patients.

Most of IgG positive patients had hypertension and atrophy diseases, whereas, IgM positive patient had atrophy disease (Table 2). About 75% of positive IgM cases were administrated prograf as an immunosuppressive drug, and 25% were administered cyclosporine. While in IgG positive cases, 83.92% were administrated prograf as an immunosuppressive drug, 13.29% were administered cyclosporine, and 2.79% were administrated prograf plus prednisolone drug (Figure 2).

Table 2
Association of clinical data with serological markers of Epstein-Barr virus. *n* (%).

Disease	IgG		IgM	
	Positive	Negative	Positive	Negative
Hypertension	26 (93)	2 (7)	0 (0)	28 (100)
Infection	9 (82)	2 (18)	0 (0)	11 (100)
Renal disease	4 (67)	2 (33)	0 (0)	6 (100)
Atrophy	10 (100)	0 (0)	1 (10)	9 (90)
Gout	4 (100)	0 (0)	0 (0)	4 (100)
Others	90 (97)	3 (3)	3 (3)	90 (97)

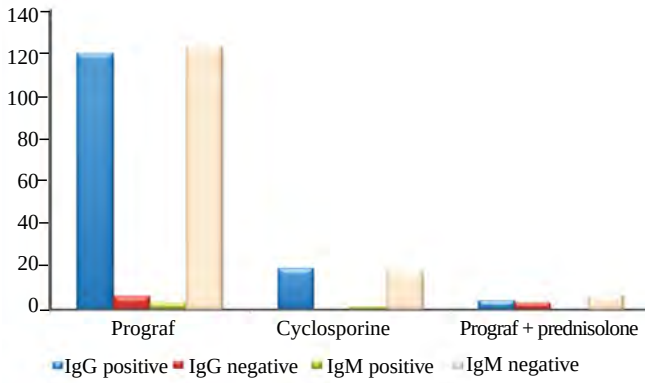

Figure 2. Association of immunosuppressive drugs with serological markers of Epstein-Barr virus.

4. Discussion

Epstein-Barr virus has a significance effect among organ transplant recipients. Post-transplant lymphoproliferative disease, is a major complication among organ transplant recipients. In the present study we shown that 71.05% of the renal transplant patients were males, 56.57% were living in cities and the percentage of renal transplant patients was increased with increasing age. In Sudan the number of transplant patients was increase every year, and 85.53% of the patients had renal transplantation in Sudan. Lauzurica *et al.*[13] indicated that no differences between patients with and without Epstein-Barr virus reactivation in relation to age, gender, type of dialysis, time on dialysis, frequency or severity of acute rejection episodes. World Health Organization report indicated that the occurrence of post-transplantation lymphoproliferative disease decreases after the first post transplant year, Epstein-Barr virus sero-negative recipients appear to have a higher risk of post-transplantation lymphoproliferative disease beyond the first post-transplant year[14,15], but the cumulative incidence increases with time[4]. Epstein-Barr virus establishes latency in B lymphocytes in association with expression of a limited set of viral genes[2].

A correlation between an increasing level of anti-Epstein-Barr virus nuclear antigen antibodies (including those introduced through transfusions) with a decrease in Epstein-Barr virus viral load has been demonstrated[16]. The presence of IgM antibody raised to the capsid antigen in the absence of antibody to the nuclear antigen is an indicator of acute primary Epstein-Barr virus infection[17]. However, false negative results may occur as a consequence of the transient nature of the viral capsid antigen IgM response. Conversely, false-positive IgM reactions can occur due to the presence of auto-antibodies, or cross-reactions with other members of herpes virus family[18].

Among 152 of renal transplant recipients studied 94% were IgG positive indicating past infection, while 3% were IgM positive indicating active infection. Similarly Morton indicated that 441 (90%) of individuals were Epstein-Barr virus seropositive, with detectable Epstein-Barr virus antibodies to viral capsid antigen and 49 (10%) were seronegative[19]. Geramizadeh *et al.*[20] showed that 11/116 (9%) of patients were viral capsid antigen IgM positive. Epstein-Barr virus sero-prevalence in western societies can be as high as 95% among adult people[21], in Turkey 99.4% were seropositivity[22]. Epstein-Barr virus seropositivity was increased with age in transplant population[23]. Previous studies recommend screening for Epstein-Barr virus DNA during the first year particularly for high risk Epstein-Barr virus donors, like sero-positive recipients and sero-negative patients[14]. High Epstein-Barr virus loads probably indicate a “net state of over immunosuppression” manifested as a reactivation of lytic Epstein-Barr virus infection[24]. Diseases associated with renal transplant patients were hypertension 18.42%, infectious diseases 7.24%, renal diseases 3.95%, atrophy 6.58%, gout 2.63% and other diseases 61.18%. Allain-Launay *et al.*[25] showed that 39.5% and 36.0% of the patients were treated for hypertension at five and ten years following transplantation[26,27]. Most IgG positive patients have hypertension and atrophy diseases, whereas, IgM positive patient have atrophy disease.

About 75% of IgM positive patients were administrated prograf and 25% cyclosporine as an immunosuppressive drug. While 83.92% IgG positive patients were administrated prograf, 13.29% cyclosporine, and 2.79% prograf plus prednisolone as an immunosuppressive drug. Previous studies showed that major complication was associated with prograf based immunosupression[28].

Conflict of interest statement

We declare that we have no conflict of interest.

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