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Seroprevelance of CMV Infection in Multi-Transfused Adult Patients with Haematological Malignancies: Single Iraqi Hematology Center Experience

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ABSTRACT

Transfusion-transmitted viral infections (hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV) and cytomegalovirus (CMV) are the most common transfusion-transmitted infections. Screening for HBV, HCV, HIV are recommended by WHO to be screened for before transfusion. The aim of the study is to determine the seroprevalence of transfusion transmitted CMV infection in a subsets of hematological malignancy patients as compared to non-transfused healthy controls. A serology for the detection of CMV IgG and IgM antibodies was done for 48 multi-transfused patients with hematological malignancies and for 96 untransfused healthy controls to determine the seroprevalence of CMV in this study which showed positive CMV IgG in 84 control subjects (87.5%) and 45 patients (93.8%) with no statistically significant association in the seroprevalence of CMV IgG and history of transfusion (P value > 0.05) while positive CMV IgM was seen in 2 control subjects (2.1%) and 10 patients (20.8%) with a statistically significant association (P value < 0.05) between the seroprevalence of positive CMV IgM with exposure to the blood products. This high prevalence result of CMV infection also mandate appropriate actions include the using of leuco-depleted filters or CMV-negative blood.

Keywords: *Seroprevalence, CMV Infection, Multi-Transfused Patients, Haematological Malignancy.*

Introduction

Blood and blood product transfusion is an integral component of medical practice and is essential in many treatments including hospitalized surgical and medical patients [1]. It is vital for a variety of patients with chronic anemia such as haemoglobinopathies and for those with coagulopathies [2]. In addition, transfusion is critical for patients with hematological malignancies undergoing aggressive treatment regimens. Transfusion of any blood product involves the risk of an adverse reaction, including disease transmission [3]. While stringent measures are being taken to minimize the risk of transfusion-transmitted viral infection, it may never be possible to guarantee that donor blood is absolutely safe [2].

Human cytomegalovirus infections commonly are associated with the salivary glands. Human cytomegalovirus (CMV) is a wide-spread virus and its infection may be asymptomatic in healthy people, but they can be life-threatening in an immunocompromised patient [4-6]. Congenital cytomegalovirus infection can cause morbidity and even death. After infection, CMV often remains latent, but it can reactivate at any time. Eventually, it causes mucoepidermoid carcinoma, and it may be responsible for prostate cancer. CMV infects between 60% to 70% of adults in industrialized countries and close to 100% in emerging countries. Of all herpes viruses, CMV harbors the largest number of genes dedicated to evading innate and adaptive immunity in the host. CMV represents a lifelong burden of antigenic T-cell surveillance and immune dysfunction. Congenital CMV is a leading infectious cause of deafness, learning disabilities, and intellectual disability [7].

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CMV is the most significant in blood transfusion, and was previously transmitted widely, with serious consequences for some patients [8]. Once CMV is transmitted, and the primary infection clears, the virus remains dormant in myeloid cells. Vital replication and reactivation are contained primarily by cytotoxic T-cell immunity. However, when reactivation occurs, virions are released into the bloodstream and other body fluids, leading to the presence of symptoms, predominantly in immunocompromised patients [7,9]. CMV can infect a wide range of cell types, including leukocytes of monocyte-macrophage lineage and their progenitors, of which the former represent the preeminent source of transfusion-transmitted infection. Consequently, cell-depleted blood components (plasma, cryoprecipitate) do not transmit CMV and infection has not been reported [10].

Primary CMV infection in immunocompetent individuals is usually community-acquired and often asymptomatic or associated with a mild, self-limited infectious mononucleosis syndrome. The incubation period generally lasts from 1 week to 1 month and antibodies appear following resolution of infection and the development of latent state of infection. However, in virtually all cases, latent virus persists permanently in cellular reservoirs, allowing lifelong reactivation infections, or in the setting of transfusion or transplantation, viral transmission via cellular blood products, or transplanted donor organs [10]. In immunosuppressed patients, CMV infection usually leads to gastroenteritis, hepatitis and pneumonitis and rarely retinitis, encephalitis and other inflammatory conditions often associated with considerable morbidity and mortality. The reported risk of (usually asymptomatic) CMV infection in seronegative immunocompetent patients who receive non-leukocyte- reduced cellular blood components unscreened for presence of CMV antibodies is approximately 1% [8]. In contrast, the historical risk of CMV infection in immunocompromised recipients receiving CMV unscreened, non-leukocyte-reduced blood components has been reported in various studies from 13.5% to 53.3% [10].

CMV seronegative tested blood is given to immunosuppressed patients who are susceptible to acquiring CMV. Selection of CMV seronegative or leukocyte-reduced blood components for susceptible patient groups have significantly reduced the risk of transfusion-transmitted CMV infection to 0-7% [16-19]. Screening for CMV is not generally applied to all donations because the percentage of patients requiring screened blood is relatively low [8].

The aim of this study was to in order to investigate the prevalence of CMV infection in immunocompromised patients by determining CMV IgG and IgM antibodies in multi-transfused adult hematological malignancies patients.

Materials and Method

A total of forty-eight patients with hematological malignancies were enrolled into this study for determination the sero-prevalence of transfusion-transmitted CMV infection by including patients in the post-transfusion period once and excluding new patients not receiving transfusion products. The baseline data requested were concentrated mainly on patient's name, age, sex, marital status, residence, the diagnosis of hematological malignancies type, comorbidity, blood group and Rh, whether the patient donate blood before or not, the type of blood product the patient received (packed red cells, platelet transfusion, cryoprecipitate or fresh frozen plasma) and any previous CMV infection. All patients in this study were compared with a control group (96 healthy donors) obtained from our local blood bank who was not previously transfused.

Anti-CMV IgG and Anti-CMV IgM ELISA kits (Biocheck, Inc., USA) were used in this study for the quantitative determination of CMV IgG and IgM antibodies in human serum or plasma. Purified CMV antigen is coated on the surface of microwells. Diluted patient serum was added to the wells and the CMV IgG or IgM specific antibodies, if present, bind to the antigen. The intensity of the color generated (yellow) is proportional to the amount of CMV IgG or IgM specific antibody in the sample. A CMV IgG index of 1.0 or greater, IU value greater than 1.2 is seropositive, whereas, > 1.2 IU/ml indicate prior exposure to the CMV. A CMV IgM index of 1.0 or greater is positive for IgM antibody to CMV. The data were analyzed by the computer software program Statistical Package for Social Science (SPSS, version 18/IBM.US./2007).

Results

Forty-eight patients were included in this study: 22 males (mean age 37.3 ± 18.33, age range 16-69 years) and 26 females (mean age 37.7 ± 15.7, age range 15-75

years) with different hematological malignancies. From all patients, there were 19 patients with acute myeloid leukemia (AML), 11 patients with Non-Hodgkin's lymphoma (NHL), 9 patients with acute lymphoblastic leukemia (ALL), 6 patients with chronic lymphocytic leukemia (CLL) and 3 patients with plasma cell myeloma, or called multiple myeloma (MM). Female to male ratio, number and percentage of patients under study with different hematological malignancies are shown in Table (1), and figure (1). The demographic and clinical characteristics of all patients are shown in Table (2).

Table 1: Distribution of patients under study according to sex and age

Sex	Number (%)	Age	
		Mean ± SD	Range
Male	22 (46%)	37.3 ± 18.33	16-69
Female	26 (54%)	37.7 ± 15.7	15-75
Total	48 (100%)	57.5 ± 16.8	15-75

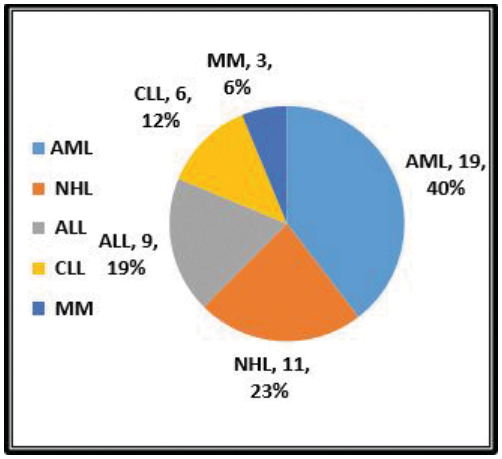

Figure 1: Distribution of patients under study according to the type of hematological malignancies

The Seroprevelance of CMV infection in this case-control study which include 96 healthy untransfused donor population as control and 48 patients showed that positive CMV IgG was seen in 84 control subjects (87.5 %) and 45 patients (93.8%) under study. There was no statistically significant association in the seroprevalence of CMV IgG and history of transfusion (P value > 0.05). Positive CMV IgM was seen in 2 control subjects (2.1 %) and 10 patients (20.8 %) under study. There was statistically significant association (P value < 0.05) between the seroprevalence of positive CMV IgM with recent exposure to the blood products. The positive results for both CMV IgG and IgM antibodies which indicated by ELISA in all patients and control group are shown in Table (2), Figure (2).

Table 2: Sero-prevalence of CMV IgG and IgM antibodies in all patients under study compared with control group

CMV		Patients	Control	Total	P. Value
IgG	+ve	45 (93.8%)	84 (87.5%)	129 (89.6%)	P value > 0.05 (0.38)
	-ve	3 (6.3%)	12 (12.5%)	15 (10.4%)	
IgM	+ve	10 (20.8%)	2 (2.1%)	12 (8.3%)	P value < 0.05 (0.00044)
	-ve	38 (79.2%)	94 (97.9%)	132 (91.7%)	

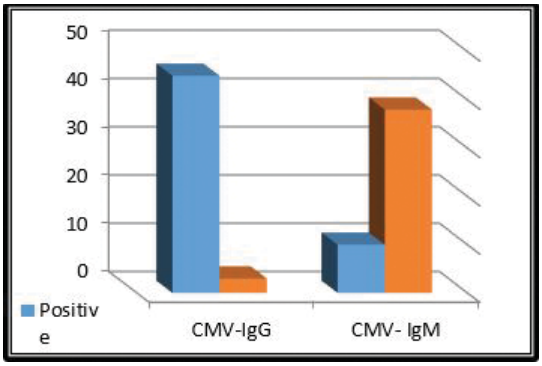

Figure 2: Sero-prevalence of CMV among all patients under study

Discussion

World Health Organization (WHO) recommended optimal blood donation screening for hepatitis (HBV and HCV), HIV and CMV. The first three viruses are recommended to be tested for before transfusion in both immunocompetent and immunocompromised patients while CMV is no usually tested but testing is recommended in the immunocompromised patients [20-22].

This study showed higher prevalence of anti-CMV IgG and IgM antibodies among patients, and these findings are comparable to that reported by Alizi [23], who found that 99.1% of the Iraqi immune-compromised patients were positive for anti-CMV IgG, and 8.4% for IgM and Omer et al [24] who found that 96% of the Iraqi immune-compromised patients with acute leukemia were positive for anti-CMV IgG, and 12% for IgM. In Egypt, Loutfy et al [25] also found a high seroprevalence of CMV antibodies in both leukemic children (100%)and their

controls (100%). The detection of a high prevalence of CMV antibodies among patients and apparently healthy Iraqi people indicates that CMV infection is endemic in our country. This supports the suggestion of CMV reactivation particularly among immunocompromised patients including leukemic patients. These results show that there are at least 3 factors that may play a role in active CMV infection among immunocompromised patients; first receiving large amount of blood ensuring transfer of viable cells latently infected with CMV. The second factor may be the course of immunosuppressive therapy in different doses depending on their disease. Lastly, this variation may be due to the pathogenesis of their diseases [26].

Prevention of CMV infection in Iraq needs the adoption of Iraqi blood banks which still not adopt CMV for screening for blood donors and to provide leukocyte-depleted filters to high risk patients (including pregnant, neonates and immunocompromised patients receiving chemotherapy) which will significantly reduce the risk of transfusion-transmitted CMV infection to 0-7% [12, 16-19].

What is the risk of CMV transmission to an already CMV seropositive individual? Contact with blood products containing CMV may cause reactivation of latent CMV virus in a state of immunosuppression. Another possibility is reinfection with a new strain of CMV, as demonstrated in patients with the human immunodeficiency virus (HIV) and organ transplant recipients [27,28].

A higher risk for a sever CMV infection has been suggested following infection with a second strain of CMV [27]. It is very difficult to assess with certainty the importance of CMV transmission by blood products into already CMV seropositive patients.

Whether CMV disease occurring in seropositive patients is more or less frequently caused by a reactivation of a previous strain or by re-infection of a new strain is unknown but is likely to be strongly influenced by the existing CMV immunity in the patient and the donor [29, 30].

For years only blood from CMV-negative donors was used to transfuse CMV-negative patients. This policy is effective in preventing CMV infection, but because 50% of the population is positive for CMV antibodies, it may potentially lead to shortages of products that could be transfused to the patient [31]. Currently, leuko-reduced blood products are used since leuko-filteration of the blood is just as effective as transfusion of CMV-negative blood in preventing infections and allows greater use of all blood products [32].

Pathogen inactivation is the newest approach for CMV inactivation making blood safer. Several technologies are already available or in development and their efficacy in inactivating CMV has led to discussions on omitting CMV testing in the future. The final choice of a technique will most likely depend on the risk for severe CMV disease in the patient population as well as the efficacy, safety and costs of the chosen techniques [12].

Conclusion

There was a high prevalence of cytomegalovirus infection in the multi-transfused patients relative to healthy untransfused patients. High prevalence of CMV infection which also mandate appropriate actions include: Use of leuko-depleted filters, use of CMV-negative blood and viral inactivation methods.

Conflicts of Interest: None of the authors have any conflicts of interest relevant to what is written.

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Ethical Clearance: The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and the subject information and consent form were reviewed and approved by a local Ethics Committee.

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