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Seroprevalence of Human Herpes Virus 8 among Blood Donors in National Blood Centre, Kuala Lumpur, Malaysia

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Authors' contributions

This work was carried out in collaboration between all authors. Author KWS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors MNA, MN, MYA, ATNS and KR wrote the first draft of the manuscript. Authors KWS and MNA carried out the statistical analysis. Authors KWS, MNA, MN, MYA, AN, AY and MYN read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: In South East Asia, there is no regional or local HHV-8 seroprevalence data on blood donors. Thus this study was aimed to determine the seroprevalence of HHV-8 among blood donors in National Blood Centre, Kuala Lumpur (NBCKL) and to test its association with donor socio demographic and transfusion transmitted infection (TTI) seropositivity.
Study Design: A cross sectional study.
Place and Duration of Study: National Blood Centre, Kuala Lumpur (NBCKL). Duration of the study from January 2008 to June 2009.
Methodology: A total of 761 serum samples were collected of which 670 from blood donors who were non-reactive for TTIs while 91 were from blood donors who were reactive for TTIs were tested for HHV 8 using BIOTRIN HHV-8IgG EIA kit and BIOTRIN

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HHV-8IgG Immuno fluorescent assay (IFA).
Results: The HHV-8 seroprevalence among blood donors in NBCKL was 1.3% (10/761) of which 0.9% (6/670) among healthy blood donors and 4.4% (4/91) among TTI seropositive donors. TTI seropositivity (p=0.023) and gender (p=0.018) shows a significant risk factors contributed to HHV-8 seropositivity. Human Immunodeficiency Virus (HIV) and Hepatitis C were associated with an increased risk of HHV-8 seropositivity (OR 6.8; 95% CI, 0 to 0.2 and OR 10.0; 95% CI, 0.1 to 0.4 respectively).
Conclusion: HHV-8 has a low seroprevalance among blood donors in the NBCKL with a male predominance. A donor with seropositivity for TTI, is associated with a higher risk HHV-8 seropositivity.

Keywords: Human herpes virus 8; transfusion transmitted infection, seroprevalance; blood donors.

1. INTRODUCTION

Transfusion transmissible infections (TTIs) are myriad of pathogens such as bacteria and viruses that can be transmitted through blood transfusion. Different strategies and approaches have been adopted by Blood Transfusion Service (BTS) worldwide to reduce the risk of TTIs and to provide the safest blood supply. One of the strategies is by screening of blood [1]. Globally, only four infections (HIV, Hepatitis B, Hepatitis C and Syphilis) are deemed to be universally screened by WHO [2]. Human herpes virus 8 (HHV8) is considered as one of the emerging infectious agents which threatens blood safety. However, it is not routinely screened for. HHV-8 is also known as Kaposi's sarcoma associated herpes virus (KSHV), a human oncovirus that was first discovered by Chang et al. [3] by representational difference analysis of Kaposi's sarcoma biopsies. Kaposi's sarcoma is a cancer that causes patches of abnormal tissue to grow under the skin, in the lining of the mouth, nose, and throat or in other organs.

HHV-8 is a rhadinovirus (γ2-herpesvirus) has an amorphous tegument and a lipid bilayer which surround a protein capsid structure within. It is a large double stranded DNA virus measuring 120 to 140 nm with more than 90 genes coded by a 140 kilobase (kb) long unique region (LUR) flanked by 801 base pair (bp) terminal repeat units. The viral genes are divided into 3 types: 1) genes common to all herpesviruses (conserved regions), 2) genes uinique to HHV-8 (Non-conserved regions) and 3) genes that are homologous to cellular genes [4].

The epidemiology of HHV-8 varies among different countries and among different regions within the same country as well as variation across different population groups. It has been reported to be highest in Africa where Kaposi's sarcoma is endemic, high in Southern European and Middle Eastern Mediterranean populations and lowest in Asia, United States and Western Europe [5]. In one of the earliest HHV-8 seroprevalence studies which included Thailand and Malaysia, the seroprevalence was found to be low at 4.4% [6].

HHV-8 can be transmitted through sexual and non-sexual contact [7]. Non sexual transmission of the virus can be transmitted via close contact, parenteral route such as intravenous drug users, blood transfusion and also via transplantation [7,8]. Blackbourn et al. recovered the possibility of KSHV transmission by blood transfusion from a single blood donor and were able to propagate the virus in previously uninfected target cells [9]. More compelling evidence to support the transmission of HHV-8 by blood transfusion was

provided by a study out in Uganda linking blood donors and transfusion recipients. In this study, they found that HHV-8 seronegative transfusion recipients were more likely to seroconvert after having received blood from seropositive blood donors than the recipients of seronegative blood [10].

In the past, the test employed to conduct HHV-8 seroprevalence studies include enzyme immunoassay (EIA) and immunofluorescent assay (IF) for latent and lytic antibodies as well as immunoblot. Abalashi et al. [6] utilized whole virus EIA to detect HHV-8 anti-lytic IgG antibody in one of the earliest seroprevalence studies carried out. The use of EIA and IFA was in stark contrast to the more sophisticated tests currently in use due to the advent of new molecular techniques and its application in HHV-8 seroprevalence studies such as polymerase chain reaction (PCR). However, serological assays have been proved to be more practical for epidemiology studies and HHV-8 infection especially for detecting previous exposure to the virus due to its high sensitivity [11].

In Malaysia, there is no regional or local HHV-8 seroprevalence data on blood donors. Clearly there is a gap of knowledge in this area which has public health implications. The question of whether or not we should screen our blood for HHV-8 begs to be answered as previous studies have found that HHV-8 could possibly be transmitted via blood transfusion [12]. Thus, this study was carried out to determine the seroprevalence of HHV-8 among blood donors in The NBCKL and the association between HHV-8 seropositivity with sociodemographic and TTI seropositivity.

2. MATERIALS AND METHOD

2.1 Collection Centre

This study was conducted at The National Blood Centre, Kuala Lumpur (NBCKL) from 1st January 2008 until 30th June 2009.

2.2 Data Collection

A total of 761 serum samples were selected from the total 221,572 units collected over the period of 18 months from the blood donors. All samples came from registered blood donors that were recruited at NBCKL and mobile clinics in accordance to standard operating procedure (SOP). All blood donors that were eligible to donate and agreed to participate in this study were given a standardized pre donation questionnaire which was self-administered. Then, a face to face interview was carried out in private and confidential settings. The interviewers went through each and every item in the questionnaire with the donors. This was followed by brief medical examination consisting of general appearance inspection, blood pressure measurement, donor's weight and hemoglobin level determination. Information regarding donor's identity and donation history were recorded in record cards, registration form, donor certificate book and also Blood Banking Information System (BBIS) to facilitate access and retrieval for references and other purposes. Written consent was obtained from the donors prior the interview. This study was approved and supported by Advance Medical and Dental Institute (AMDI) and Universiti Sains Malaysia (USM) and NBCKL. Ethic approval was granted by Medical Research Ethics Committee (MREC), Ministry of Health, Malaysia (MOH) (NMRR 08-18-1173).

Sample size was calculated using Epi-Info Version 6 and epidemiological statistical software developed by CDC. Using an expected frequency of 4% and the worst acceptable frequency of 2.5%, the sample size was calculated to be 656 with a confidence level 95% (Abalashi 1999). Selection of samples was performed by simple random sampling method. From these, 670 samples were found non-reactive to TTIs and 91 samples were found reactive to TTIs. Confirmatory tests were carried out includes line immunoassay for HIV, neutralization test for Hepatitis B, recombinant immunoblot assay (RIBA) for Hepatitis C and Treponema pallidum particle agglutination (TPPA) test for syphilis.

2.3 Specimen Collection

Eight ml of blood was collected from blood donors and was put in plain vacutainer (Vacuette serum tubes containing Z serum separation clot activator). Blood was withdrawn via venepuncture as per Standard Operating Procedure (SOP) by medical officer or phlebotomist. Serum sample was screened for TTIs and remaining serum samples were kept frozen (at -20℃) until testing was performed for HHV-8.

2.4 Serological Testing

All blood donors were screened for reactivity to TTIs. Confirmatory test for TTIs were carried out on all reactive donors. The qualitative detection of HHV-8 antibodies in human serum specimens was done using BIOTRIN HHV-8IgG EIA kit, which is a direct enzyme immunoassay as per manufacturer's instruction. The HHV-8IgG EIA method can be found in the product manual that was supplied for each HHV-8 EIA kit (Biotrin A; Biotrin B). The index value facilitated data between different assay runs and it determined the positivity or negativity of a sample. Samples were considered reactive if the index value was more than 1.2, whereas non-reactive samples had index value of less than 0.8. Samples were considered equivocal if they were neither reactive nor non-reactive and then they were re-tested. If the index value was still equivocal after re-testing, the sample was tested with BIOTRIN HHV-8IgG Immuno fluorescent assay (IFA). The negativity or positivity of the reaction is determined by the grading of the IFA reaction. Test samples were considered negative for HHV-8IgG antibodies if fluorescent staining of the infected cells was absent while a green fluorescent staining of the infected cells indicated a positive reaction.

2.5 Statistical Analysis

Descriptive statistics for basic characteristics of the donors were carried out and univariable analyses where Pearson chi-square tests were performed to test associations between sociodemographics, TTIs and HHV 8 seroprevalence. A multiple logistic regression analysis was used to determine the predictor for this study. The result was considered statistically significant if the p value was less than 0.05 ($P<0.05$). Statistical analyses were performed by using SPSS version 17.0.

3. RESULTS AND DISCUSSION

3.1 Blood Donors

A total of 221,572 units of whole blood were collected by NBCKL between the month of January 2008 and June 2009. All blood donors donated on a voluntary and Non-remunerated basis. The blood donors were made up of a wide spectrum of donors which

included new donors, repeat donors, whole blood donors, plasmapheresis and plateletpheresis donors who donated at NBCKL or at mobile sessions. They came from a diverse socio-demographic background in terms of gender, race, age, marital status and occupation. From these donors, 761 were selected by simple random selection and screened for HHV 8.

3.2 Socio Demographic Factors

Basic characteristics for this study shows that out of 761 donors screened, 511 (67.2%) of the subjects were males. Majority of the respondents were Malays that consists of 432 (56.8%), followed by 224 (29.4%) Chinese, 76 (10.0%) Indian and others, 29 (3.8%). The age of the donors ranged from 18 to 60 years, with a mean of 32.48 years. About 366 (48.1%) of the respondents were aged 21-30 years. 450 (59.1%) of the study population are single, 305 (40.1%) married and 6 (0.8%) divorced. In term of occupation, 257 (33.8%) were professionals, 223 (29.3%) were unskilled workers and less than 20% are unemployed (17.7%) and semi-professional (19.2%). More than 50% (396, 52.0%) of the donors were repeat donors and 365 (48%) were new donors.

Most of the donors donated whole blood (93.2%) and 6.8% donated apheresis. Eighty three percent of donors donated at blood mobile sessions and 16.8% at NBCKL. Blood group O, 317 (41.7%) dominated among the donors followed by 222 (29.2%) group B, 168 (22.1%) group A and 54 (7.1%) group AB. Details for basic characteristics for this study were depicted in Table 1.

3.3 Seroprevalence of HHV-8

Out of the 761 donors screened, only 10 donors were found to be HHV-8 seropositive giving a seroprevalence rate of 1.3% among blood donors. The racial distribution of HHV-8 seropositivity donors include 7 (1.6% of Malay donors) Malay, 1(0.4% of Chinese donors) Chinese, 1(1.3% of Indian donors) Indian and 1 (8.3% of donor who were non-Malaysian) foreigner.

Six of the HHV-8 seropositive donors belonged to the age range of 21-30 years, 2 were in the range of 31-40 years, and 1 donor each in the ranges of 41-50 years and 51-60 years age group. The HHV-8 seropositive donors were made up of 50% unskilled workers, 20% professionals, 20% unemployed and 10% a semi-professional. Interestingly, the majority of the HHV-8 seropositive donors were single (80%) and 60% were new donors.

3.4 HHV-8 seropositivity with Socio Demographic

Univariable analysis Table 2 shows that only gender and seropositivity for TTIs have a significant association with HHV-8 seropositivity. All 10 donors of HHV-8 seropositive in this study were males (P=0.018). There was no significant difference in age between HHV-8 seropositive donors and HHV-8 seronegative donors, with p value of 0.624. Other socio demographic factors such as race, age group, marital status and type of donors were not significantly associated to HHV-8 seropositivity.

Table 1. Basic characteristics among blood donors

Variable		Frequency (N =761)	Percentage (%)
Sex	Male	511	67.1
	Female	250	32.9
Race	Malay	432	56.8
	Chinese	224	29.4
	Indian	76	10.0
	Others	29	3.8
Age	≤20	17	2.2
	21–30	366	48.1
	31–40	219	28.8
	41–50	131	17.2
	51–60	28	3.7
Marital status	Single	450	59.1
	Married	305	40.1
	Divorced	6	0.8
Occupation	Unemployed	135	17.7
	Unskilled worker	223	29.3
	Semi professional	146	19.2
	Professional	257	33.8
Type of donor	New donor	365	48.0
	Repeat donor	396	52.0
Type of donation	Whole blood	709	93.2
	Apheresis	52	6.8
Blood group	A	168	22.1
	B	222	29.2
	O	317	41.7
	AB	54	7.1
HHV-8 seropositivity	Seropositive	10	1.3
	Seronegative	751	98.7
Seropositivity for TTIs	Non-reactive	670	88.0
	HIV reactive	13	1.7
	Hepatitis B reactive	12	1.6
	Hepatitis C reactive	34	4.5
	Syphilis reactive	32	4.2

Table 2. Relation between socio demographic factors and HHV-8 Seropositivity

Variable		HHV-8 Seronegative n (%)	HHV-8 Seropositive n (%)	df	x^2	p Value*
Gender	Male	501 (98.0)	10 (2.0)			
	Female	250 (100.0)	0 (0.0)	1	4.96	0.018
Race	Malay	425 (98.4)	7 (1.6)			
	Non Malay	326 (99.1)	3 (0.9)	1	0.72	0.304
Age	≤ 25 years old	201 (97.6)	5 (2.4)			
	>25 years old	550 (99.1)	5 (0.9)	1	2.7	0.103
Marital status	Single	442 (98.2)	8 (1.8)			
	Married	303 (99.0)	2 (0.7)	1	0.588	0.327
Type of donor	New donor	359 (98.4)	6 (1.6)			
	Repeat donor	392 (99.0)	4 (1.0)	1	1.701	0.164
Seropositivity for TTIs	Non-reactive	664 (99.1)	6 (0.9)			
	Reactive	87 (95.6)	4 (4.4)	1	7.57	0.023

**Pearson's Chi Square test: significant if P<0.05*

3.5 HHV-8 Seropositivity with TTI Seropositivity

As for the seropositivity for TTIs, 670 donors (88.0%) were non-reactive as compared to 91 donors (11.9%) who were reactive for TTIs that include of 13 donors that were HIV reactive (1.7%), 12 donors that were Hepatitis B reactive (1.6%), 34 donors that were Hepatitis C reactive (4.5%) and 32 donors that were Syphilis reactive (4.2%). Six donors non-reactive for TTIs and 4 donors reactive for TTIs were HHV-8 seropositive. The seroprevalence of HHV 8 was significantly higher in donors with TTIs with p value of 0.023. Among the TTIs seropositive donors with HHV 8 seropositivity were 3 donors reactive for hepatitis C (8.8% of hepatitis C reactive donors) and 1 donor reactive for HIV (7.7% of HIV reactive donors). None of the HHV-8 seropositive donors were reactive for syphilis or hepatitis B.

3.6 Risk of Getting HHV-8

In the final model Table 3. after multivariable analysis were carried out, the predictor for this study is seropositivity for TTIs with p value of 0.02 at 95% CI (-0.486, -0.821). Donors reactive for TTIs were 5 times at higher risk of HHV-8 seropositivity compared to those who were seronegative for TTIs (OR 5.1; 95% CI, -0.5 to -0.1).

HIV and hepatitis C were both significantly associated with an increased risk of HHV-8 (OR 6.8; 95% CI, 0 to 0.2 and OR 10.0; 95% CI, 0.1 to 0.4 respectively), and the risk was higher if the donor was hepatitis C seropositive than if the donor was HIV seropositive Table 4.

Table 3. Multivariable analysis: Predictor for HHV-8 Seropositivity

Variable	B	df	Adjusted Odd Ratio	p Value†	95.0% C.I.for exp(B)	
					Lower	Upper
Gender	0.015	1	0.062	0.093	-	-
Seropositivity for TTIs	0.030	1	5.1	0.02	-0.486	-0.821

†Multiple logistic regression, p is significant when < 0.05

Table 4. Odds ratio of TTI seropositivity, HIV and hepatitis C

	Odds ratio	95% Confidence interval of the difference	
		Lower	Upper
TTI seropositivity	5.1	-0.486	-0.821
HIV	6.8	0.003	0.165
Hepatitis C	10.0	0.131	0.387

4. DISCUSSION

The majority of blood donors in this study were male donors, 67.1%. The result showed that 100% of the HHV-8 seropositivity was present in male donors. Male gender was significantly associated with HHV-8 ($P<0.05$). Mwakigonja et al. [13] gave a similar finding of male predominance. They suggested that there could be a biological basis for male susceptibility to HHV-8 as there observed cytogenetic changes such as loss of Y chromosomes in early KS in males. In another study, it was found that male gender is risk factors for HHV-8 infections [14]. The gender differences in the HHV-8 seropositivity could be due to socio-behavioural factors [13]. Interestingly 95% of deferred donors in NBC due to high risk behaviour were males [15] lending credence to this theory.

In this study, 4.4% (4 out of 91) of TTI seropositive donors were HHV-8 seropositive. TTI seropositivity was significantly associated with HHV-8 ($p<0.05$). At the multivariate level, TTI seropositivity was found to be a bigger contributor to HHV-8 than gender. Upon calculation of odds ratio, TTI seropositive blood donors had an odds ratio of 5.1 to acquire HHV-8 (OR 5.1; 95% CI -0.5 to -0.1). These findings were supported by previous study where HHV-8 seropositivity was significantly associated with HIV seropositivity13. Suchankova et al. [16] also found that HIV positive individuals had an even higher odds ratio of 18.6 to acquire HHV-815. Sosa et al. [17] concluded that HHV-8 share the same route of transmission with Hepatits B and C which is via sharing of contaminated needles. In Malaysia, majority of hepatitis C cases (85%) are due to intravenous drug use [18], which could explain the significant association between TTI seropositivity and HHV-8 as was found in this study.

From this study, overall seroprevalence of HHV-8 among blood donors in NBCKL was found to be very low at 1.3% (10 out of 761). This is much lower than the seroprevalence of HHV-8 in Malaysia as previously reported by Abalashi, 4.4% [6]. This is not surprising as Malaysia and the countries around this region are not endemic for KS [19] unlike in East and Central Africa where KS is considered a long-standing endemic disease with seroprevalence of HHV-8 as high as 50 to 60% [20]. In NBCKL, all blood is screened. One is required to be healthy and free from any medical illness to be a blood donor. However there are still chance of missing the viral markers as the anti-viral titer and viral load are expected to be low in infected individuals who are healthy and immunocompetent [21]. They were probably not picked up by the EIA screening for HHV-8, which explains the low seropositivity rate of 0.9% (6 out of 670) among healthy blood donors in this study. It is thus possible that the tests used in this study might have underestimated the actual seroprevalence of HHV-8 among blood donors. That being the case 1.3% is actually the crude seroprevalence of HHV-8. The fact that all the donors at NBC are voluntary non-remunerated donors probably contributed to the low seroprevalence of HHV-8 in this study. Past experience has taught us that voluntary non-remunerated donors have the lowest incidence of disease markers and WHO designated donations from these donors as to be far and away the safest form of blood donation [22].

As regular non-numerated donors are the starting point of a safe blood supply, continuing effort should be made to achieve a fully non-numerated based blood pool and to increase the pool of regular donors in Malaysia. Apart from that, stringent blood screening criteria should also probably contribute to the low seroprevalence of HHV-8. Because high risk behaviour is associated with an increased risk of HHV-8 seropositivity [8], deferring donors with high risk behaviour presumably resulted in the low seroprevalence of HHV-8 among blood donors in NBC. High risk behavior includes of homosexual where study reported by Zago et al. [14] showed a significant association between homosexuality and higher seroprevalence rate of HHV-8 compared to general population. Zago et al. [14] and Suchankova et al. [16] found that bisexuality is also a risk factor for HHV-8. Sexual promiscuity, number of sex partners, having sex with sex workers and injecting drug users (IDUs) were reported as a risk for HHV-8 sepositivity [7,8,17].

In a country non-endemic for KS such as Malaysia, multiple risk factors are a more important predictor for HHV-8 infection especially in a healthy population such as blood donors. However, this theory of multiple risk factors acting synergistically to increase the risk of HHV-8 cannot be proven from this study due to the small number of HHV-8 seropositive donors. For that reason, a study with a bigger sample size of TTI seropositive donors with multiple risk factors will need to be carried out in order to allow for greater statistical power to establish the association of multiple risk factors with HHV-8 seropositivity.

The question is whether to screen donated blood for HHV-8 for at risk groups such as immunocompromised groups is debated. In South Africa, Stein et al found it prudent in the setting of high seroprevalence of HHV-8 to screen donated blood to be transfused to these individuals [4]. This argument seems rational as the high seroprevalence of HHV-8 among blood donors corresponds with the high seroprevalence among the general population. However, this is not the case in Malaysia. So screening of blood donors for HHV-8 is probably unwarranted as it is impractical and not cost effective.

A total of 221 572 units of whole blood were collected by NBC during this study period. Out of the 709 donors who donated whole blood, 9 (1.3%) donors were HHV-8 seropositive. This means that approximately 2 813 (1.3% x 221 572) units of whole blood were probably collected from donors who were potentially HHV-8 seropositive. One wonders how many of these 2 813 units of blood were transfused to groups at risk of KS, in particular immunocompromised patients needing multiple transfusion.

However, at the moment NBC practices leukodepletion only for selected groups of patients which include transfusion-dependent patients such as patients with thalassemia, patients undergoing hematopoietic stem cell transplantation, neonates and for exchange transfusions. The efficacy of leukodepletion for reducing HHV-8 in blood has been reported [23]. Therefore it is a more practical approach to safeguard our blood supply and to ensure the safety of transfusion recipients. Hence, it would seem rational for NBC to adopt universal leukodepletion which is a step in the right direction for the BTS in Malaysia.

5. CONCLUSION

HHV-8 has a low seroprevalance among blood donors in the NBCKL with a male predominance. Donors reactive for TTIs are at higher risk of HHV 8 seropositivity.

CONSENT

Written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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