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Human T Lymphotropic Virus-I (HTLV-I), the Causative Agent of Acute T-Cell Leukaemia/Lymphoma, Is Absent among Blood Donors in Aseer Region, Saudi Arabia

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Abstract. Since the 1990s, antibodies to human T-lymphotropic virus type I (anti-HTLV-I) have been screened in units of blood donors at blood banks in Kingdom of Saudi Arabia (KSA). HTLV-I was the first human retrovirus to be discovered which naturally infects $CD4^+$ T lymphocytes and can be transmitted through blood transfer or from mother to infant through cells in breast milk. In most cases, the infection is harmless but may develop a type of adult T-cell leukemia in which every tumor cell carries a clonally integrated HTLV-I provirus.

The aim of this study was to determine the prevalence of anti-HTLV-I/II antibodies in blood donations at Aseer region, KSA, and to compare the results with other reports from different localities in KSA, as well as the cost effectiveness of anti-HTLV-I/II antibodies screening.

A 4432 blood units collected from blood donors at Aseer region were tested for the presence of anti-HTLV-I/II using enzyme-linked immunosorbant assay (ELISA). There was no seropositive case in the tested blood units.

Therefore, Aseer Region appears to be a non-endemic area for HTLV-I/II. Also, the current practice of screening all blood donors for anti-HTLV-I/II should be reviewed all over the Kingdom as it does not seem to be cost-effective.

Key words: HTLV; Blood donors; Saudi Arabia; Retrovirus; T-cell leukaemia; Lymphoma

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1. Introduction

Human T-cell lymphotropic viruses type 1 (HTLV-I) and type 2 (HTLV-II) are closely related human complex deltaretroviruses. Infection with HTLVI has been shown to develop adult T-cell leukemia/lymphoma (ATL/ATLL), and a clonal aggressive malignancy of $CD4^+$ T lymphocytes. HTLV-I is also the causative agent of a distinct neurological disorder known as HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1]. HTLV-I was the first human retrovirus to be discovered and is endemic in certain areas of the world like Japan, the Caribbean, parts of Africa, and South America where up to 10% or more of the population may be infected [2]. In the UK, HTLV-I was estimated to cause about 25 cases of acute T-cell leukaemia/lymphoma in 2010 [3].

HTLV-II was first identified in a T-cell line established from a patient with hairy-cell leukemia [4]. In addition, HTLV-II infection has been associated with sporadic cases of a myelopathy resembling HAM/TSP [5-7] but has not been clearly linked with the development of lymphoproliferative disorders. HTLV-II infection is highly concentrated in Central and West Africa [8,9], native Amerindian populations in North, Central, and South America [10-13], and among cohorts of intravenous drug users (IVDUs) in the United States and Europe [14-18].

Currently, two new types, HTLV-3 and HTLV-4, were identified [19-21].

HTLV-I naturally infects $CD4^+$ T lymphocytes and can be transmitted between close contacts through blood transfer or from mother to infant through cells in breast milk. The infection is harmless in most cases. However, as many as 1 in 20 infected individuals eventually develop a type of adult T-cell leukaemia in which every tumor cell carries a clonally integrated HTLV-I provirus [22].

HTLV-1 and HTLV-2 have a similar genome structure and share approximately 70% nucleotide sequence homology. In addition to the essential viral genes *gag*, *pol*, and *env*, HTLV-1 and HTLV-II encode regulatory and accessory genes from pX region open reading frames (ORFs) found in the 3' portion of the viral genome. ORFs IV and III encode the Tax and Rex regulatory proteins, respectively. Tax acts in *trans* to activate transcription initiating from the viral promoter in the U3 region of the long terminal repeat [23-28] and Rex regulates viral gene expression post-transcriptionally by facilitating the cytoplasmic expression of the incompletely spliced viral mRNAs [29]. HTLV-1 ORFs I, and II encode the accessory proteins p12/p27 and p13/p30, respectively, whereas the HTLV-2 ORFs I, II, and V encode the p10, p28, and p11 accessory gene products, respectively. The functional roles of these proteins in HTLV biology are not clearly understood. However, studies have indicated that they are dispensable for infection and transformation of activated T-cells *in vitro* [1], but are important for the ability of the virus to infect, spread, and persist *in vivo* [30-33].

The mechanism of action of HTLV-I differs from the standard "chronically oncogenic" and "acutely oncogenic" retroviruses as it appears to drive cell growth through expression of a particular viral protein, Tax, in latently-infected cells. Tax can transactivate expression of a number of key cellular genes that enhance cell growth. The best examples are the genes encoding interleukin-2 (IL-2) and the IL-2 receptor. Consequently, the infected cells not only make their own growth factors, but also respond to them [34-38].

The present study was designed to screen the sera collected from blood donors at southern part of Saudi Arabia for the presence of HTLV-I/II and evaluate the cost-effectiveness of performing such assay in blood banks found in the kingdom of Saudi Arabia.

2. Patients and Methods

2.1. Study Population

The study was conducted on 4432 random blood samples collected from healthy blood donor volunteers, who were referred to Blood Transfusion Centers found at Aseer Region (Southern part of KSA), during the period from March to October 2012. According to routine practice, volunteer blood donors were interviewed (history of intravenous drug abuse, jaundice, admission to fever hospital, and history of HBV vaccination) and medically examined before donation. Those with high-risk behaviour including intravenous drugs abusers, history of promiscuous sexual relationships, homosexuals, homeless, those with any medical problem especially jaundice, hospitalization at fever hospitals, bleeding disorders necessitating component transfusion, pregnancy, or recent delivery less than 12 weeks were rejected.

2.2. Detection of Anti- HTLV-I/II Antibodies

All blood specimens were tested on sequential basis for routine serological tests after singing of informed consent. The routine serological tests according to predefined protocol of blood banking safety requirements by Saudi Ministry of Health comprised HBsAg, anti-HBc antibodies (Abs), anti-HCV-Abs, anti-HIV-1/2-Abs, anti-HTLV-I/II-Abs, and Treponema Abs as well as Nucleic acid test (NAT) technology for HCV-RNA, HBV-DNA, and HIV-RNA. Detection of anti-HTLV-I/II-Abs was done using a qualitative enzyme immunoassay for the detection of antibodies against human T-lymphotropic virus types I and II in serum and plasma (DiaSorin, S. P. A. UK Branch, Central road, Dartfod DA1 5Lr, UK).

2.3. Biochemical Tests

Colorimetric determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were done according to the Reitman and Frankel method, using commercially available Randox Kit (UK). Colorimetric determination of serum urea and creatinine was done using Randox Kit.

3. Statistical Analysis

The biochemical data recorded were expressed as mean±SD and statistical and correlation analyses were undertaken using the one-way ANOVA followed by a post-hoc LSD (Least Significant Difference) test. A P value < 0.05 was statistically significant. A statistical analysis was performed with the Statistical Package for the Social Sciences for Windows (SPSS, version 10.0, Chicago, IL, USA).

4. Results

The studied samples included 4432 randomly selected blood donations from donors with a median age of 30 years. Donors of ages between 21 and 30 years constituted the largest proportion (48.71%, P = 0.001) with a median age of 24 years (**Table 1**).

Table 1: Age and number distribution of accepted blood donors for donation.

Age range	n (%)	Age (median)
18-20	292(6.59%)	20
21-30	2159 (48.71%)	24
31-40	1358(30.64%)	35
41-50	494 (11.15%)	45
51-60	129 (2.91%)	54
All	**4432 (100%)**	**30**

Table 2 lists the distribution of the nationalities of the study's participants. Blood donors were mostly Saudi nationals. Non-Saudi donors were Bengali, Egyptians, Eritrean, Indians, Filipinos, Jordanians, Lebanese, Pakistanis, Palestinians, Sudanese, and Yemenis. The higher non-Saudi proportion was Yemenis (1.33%), followed by Egyptians (0.84%), Pakistani (0.36%), Sudanese (0.24%), and then Indians (0.20%).

All donors showed normal blood pressure, pulse rate, hemoglobin level, and temperature and were voluntary non-remunerated blood donors and were qualified by a questionnaire authorized by MOH. Blood donations from 4432 males with a median age of 30 years were tested for the presence of anti-HTLV-I/II antibodies. Results showed the absence of antibodies against HTLV-I/II viruses.

The levels of ALT and AST in the serum samples were determined using commercially available kits according to the manufacturer instructions. The test was done for all donors except those showed any positive marker.

Table 2: Distribution of nationalities among accepted blood donors for donation.

Nationalities	Number	%
Bengali	1	0.022563
Egyptian	37	0.834838
Eritrean	1	0.022563
Philippines	1	0.022563
Indian	9	0.203069
Jordanian	5	0.112816
Lebanese	1	0.022563
Pakistani	16	0.361011
Palastine	2	0.045126
Saudi	4281	96.59296
Sudanese	11	0.248195
Syrian	8	0.180505
Yemen	59	1.331227
Total	**4432**	**100**

Liver enzymes levels were normal in 4259 donors (21.9±8.1 U/ml) and elevated in 173 donors (ALT 70±19.3 U/ml and AST 79.5±25.5 U/ml) (Figures 1 and 2).

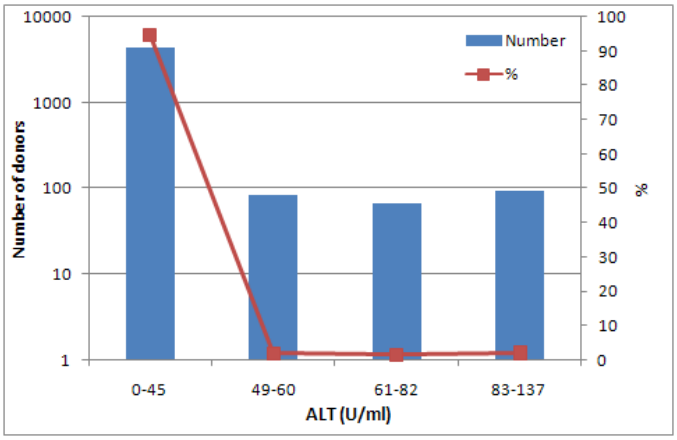

Fig. 1: ALT Level in sera of markers free donated blood.

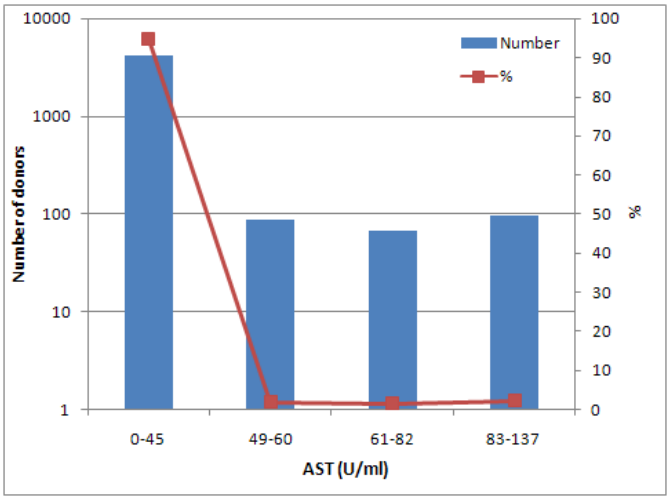

Fig. 2: AST Level in sera of markers free donated blood.

The levels of Urea and Creatinine in the serum samples were determined using commercially available kits according to the manufacturer instructions. Blood urea level was normal in 4276 donors (29.4±9.3 mg/dl) (Figure 3) and elevated in 156 donors (59.2±8.2 mg/dl). Creatinine showed normal levels.

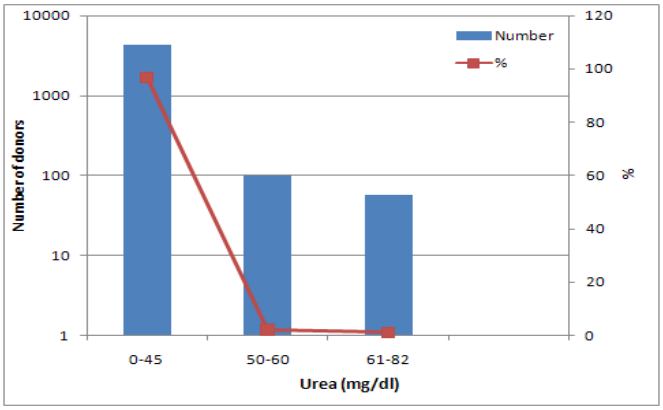

Fig. 3: Urea Level in sera of markers free donated blood.

5. Discussion

It was reported that ATL is a distinct clinical entity [39-41]. The disease which is characterized by its aggressive clinical course, infiltrations into liver, skin, lung and gastrointestinal tract, hypercalcemia and the presence of leukemic cells with multilobulated nuclei. In 1980, the human retrovirus was discovered by Poiesz *et al*[42] in a cell line derived from a patient with ATL, and designated it human T-cell leukemia virus type I (HTLV-I) [43]. Later, Hinuma *et al*[44] proved the linkage between ATL and HTLV-I by demonstrating the presence of an antibody against HTLV-I in patient sera. The whole sequence of HTLV-I was then determined by Seiki *et al* [45] revealed the presence of a unique region, designated pX. The pX region encodes several accessory genes, which control viral replication and the proliferation of infected cells [46].

In the current study, 4432 blood donors were screened for the presence of HTLV-I/II. The age range was of 21-30 years old constituted the largest population among blood donors. In addition, all the donors were male and there were no female donors during the period of this study. The percentage of non-Saudi donors was low (3.4%). A similar study

conducted on blood donors in Saudi Arabia by El-Hazmi [47] also showed that the largest group of donors were those at age range of 20-29 years old and female donors were as low as 1.2% at year 2000 and declined to reach 0.7% by year 2002. Also El-Hamzi [47] showed that the percentage of non-Saudi donors declined from 17.2% at year 2000 to reach 14.8 by year 2002.
We did not get any seropositive case in screened donated blood either in Saudi or non-Saudi blood donors.

In a chronological order **(**Table 3), Bernvil *et al* [48] screened blood donors (12,851 of which 42.6% were Saudi nationals) during the period of 1990-1991 at King Faisal Specialist Hospital and Research Center, Riyadh, KSA, and found 2 positive cases by ELISA, both donors were expatriates from North America and confirmed negative by western blot analysis. In 1998, Arif and Ramia [49] screened 5900 Saudi blood donors over a 3-year period (1993-1996) at King Abdulaziz University Hospital, Jeddah, KSA, and found zero positive cases by ELISA. While Fathallah *et al* [50] screened 40,013 blood donors from Eastern Province of Saudi Arabia, of which 33,908 were Saudis, 2065 from other Middle Eastern nationals, 2875 Asians and 1165 from other nationalities during the period from July 1995 to December 1997. They found 24 repeatedly reactive specimens by ELISA screening assays. After blotting confirmatory analysis, 9 specimens were positive, all from Saudi citizens, 4 were indeterminate, and 11 were reported as negative to HTLV-I. A study by Al-Jaouni [51] at King Fahad Armed Forces Hospital, Jeddah, between September 1995 and October 1998 included 9949 Saudi blood donors in addition to 30 patients with chronic renal failure on hemodialysis showed that none of the multitransfused hemodialysis patients had detectable antibodies to HTLV-I/II while 19 of the blood donor tested reactive by EIA. After

blotting confirmatory analysis, 3 gave negative results, and fourteen were indeterminate. In 2003, Taha *et al* [52] did a 7-year retrospective review of blood bank records for results of serological tests at the King Fahd Hospital of the University, Al-Khobar, KSA, from January 1995 to December 2001. The number of Saudi blood donors during this study was 16434 (80.3%) and non-Saudi donors were 4027 (19.7%) (total number is 23493). A total of 50 units were found repeatedly reactive by ELISA. Only 12 were confirmed reactive by western blot test and 4 were found to be indeterminate. Nine of the confirmed samples were from Saudi nationals. All 3 non-Saudi confirmed reactive donors were Indian nationals, while the 4 indeterminate cases, 2 were Saudis and 2 were Egyptians. In 2004, El-Hazmi [47] screened 24173 blood donors (23952 males and 221 females), 20423 Saudi, and 3750 non-Saudi blood donors, over a period of 3 years from January 2000 to December 2002 at King Khalid University Hospital, King Saud University, KSA, and found zero positive cases.

Also in 2004, UI-Hassan *et al* [53] studied 47426 blood donors at the Department of Laboratory and Blood Bank, King Fahad Hospital, Al-Hofuf, Al-Hasa, KSA, during the period from 1997 to 2003. Overall, HTLV-I antibody positivity (confirmed by western blot) was 3/47426. Out of 3 donors positive for HTLV-I antibody during 1997 to 1998, 2 were expatriates (Indian) and one was native Saudi donor. None of the donors was positive for HTLV-II antibody. During the last 5 consecutive years of the study period (1999-2003), none of the donors was positive for HTLV-I/II antibody. Finally, Gahzi [54]studied the results of 4 hospital found in the city of Makka. The serological markers of HTLV-I/II were studied in 5700 Saudi male blood donors. The results showed that the prevalence rate of HTLV-I/II was zero among Saudi blood donors in Makkah.

From these comparative studies we can see that the number of HTLV-I/II positive donors is chronologically in decrease order. While it is very low prevalence among Saudi blood donors, it does not support routine screening of Saudi blood donors for HTLV-I/II, screening of blood donors from other nationalities may be exercised, especially those from HTLV-I/II endemic areas [55]. We also noticed that there are many commercial ELISA detection kits available in the market. As the prevalence of HTLV-I/II infection is low, it is crucial to limit the number of samples and to choose assays that allow the dilution caused by the pooling. In a study done by Andersson *et al* [56] in which they evaluated a straight forward pooling strategy for antibody screening of HTLV-I/II, using panels of sera from various parts of the world including a total of 43 HTLV-I and 54 HTLV-II positive specimens. Four antibody screening assays were included in the evaluation. They concluded that as it is crucial to limit the number of samples and to choose assays that allow the dilution caused by the pooling. As the sensitivity of different kit varied in sensitivity ranging from dilution 1/4 up to 1/16, using the best performing assays in this evaluation for pools of e.g., four samples would leave a reasonable safety margin.

Table 3: Chronological study of the prevalence HTLV-I/II at different localities in KSA.

Authors	Period and location	Total number	number of Saudis	Positive by ELISA	Confirmed by Western blot
Bernvil *et al.*, 1991	1990-1991 Riyadh	12,851	5478 (42%)	2	0
Arif, M. and Ramia, 1998	1990-1996 Riyadh	5900	5900 (100%)	0	-
Fathallah *et al.*, 1998	July 1995 to Dec. 1997 Eastern Province of Saudi Arabia,	40,013	33,908 (85%)	24	9
Al-Jaouni, 2000	Sept. 1995 – Oct. 1998 Jeddah,	9979	9979 (100%)	19	0
Taha *et al.*, 2003	Jan. 1995 to Dec. 2001 Al-Khobar,	23493	16434 (80.3%)	50	12
El-Hazmi, 2004	Jan. 2000 to Dec. 2002 Riyadh,	24173	20423 (85%)	0	-
UI-Hassan *et al.*, 2004	1997 - 2003 Al-Hasa region	47426	N/A	3	3
Ghazi, 2006	June 2003 to May 2005 Makkah	5700	5700 (100%)	0	-
Current study	2012 Aseer Region	4432	**4281** (96.7%)	0	-

6. Conclusion

In conclusion, Aseer prevalence seems to be free from HTLV-I/II. The current practice of screening all blood donors for anti-HTLV-I/II antibody should be reviewed all over KSA as it does not seem to be cost-effective. Also, we recommend to pool at least 4 samples during the initial screening for anti-HTLV-I/II antibody to decrease the cost effectiveness of running such analysis.

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الفيروس المحب للأعضاء أليمفاوية الآدمية-1, العامل المسبب لسرطان الدم والغدد الليمفاوية, لا يوجد في المتبرعين بالدم في منطقة عسير – المملكة العربية السعودية

علي الشهري *

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المستخلص.منذ فترة التسعينات من القرن الحالي، بدأ الكشف عن الأجسام المضادة للفيروس المسبب لمرض سرطان الدم والغدد الليمفاوية النوع-1 في وحدات الدم المتبرع بها ببنوك الدم في المملكة العربية السعودية. ويعتبر فيروس سرطان الدم والغدد الليمفاوية النوع-1 أول فيروس بشري يتم اكتشافه من النوع المغلف ويحتوي على شريط واحد من الحمض النووي الرسول و الذي يصيب الخلايا الليمفاوية التائية المساعدة، والذي له القدرة على أن ينتقل عن طريق نقل الدم أو من الأم إلى الرضيع عن طريق الخلايا في حليب الثدي . في معظم الحالات، تكون العدوى بهذا الفيروس غير مؤذية ولكن قد تتطور إلى نوع من سرطان الخلايا الليمفاوية التائية المساعدة الناضجة والتي وجد في كل خلية من الخلايا السرطانية المصابة شريط الحمض النووي لهذا الفيروس ضمن مكتبة الجينات لهذه الخلايا.

الهدف من هذا البحث هو عمل دراسة عن مدي انتشار الأجسام المضادة لفيروسات سرطان الدم والغدد الليمفاوية النوع-1 و النوع-2 ومقارنة النتائج مع تقارير أخرى من مناطق مختلفة في المملكة العربية السعودية، فضلا عن فعالية الكشف عن هذه الأجسام المضادة من حيث التكلفة المضادة.

تم اختبار عدد 4432 من وحدات الدم التي تم جمعها من المتبرعين بالدم في منطقة عسير عن وجود الأجسام المضادة لفيروسات سرطان الدم والغدد الليمفاوية النوع-1 و النوع-2 بطريقة الأليزا. وأسفرت النتائج عن عدم وجود أي حالة إيجابية لوجود مثل هذه

الأجسام المضادة في وحدات الدم التي تم اختبارها. استنادا لهذه النتائج فيمكن القول أن منطقة عسير يبدو أنها منطقة غير مستوطنة بفيروسات سرطان الدم والغدد الليمفاوية النوع−1 و النوع−2. كذلك، يمكن القول بأنه ينبغي إعادة النظر في الممارسة

الحالية المتمثلة في فحص جميع المتبرعين بالدم لمكافحة فيروسات سرطان الدم والغدد الليمفاوية النوع-1 و النوع-2 في جميع أنحاء المملكة لأنه يبدو أن هذا الكشف مؤثر من حيث التكلفة.

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