Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Frequency of Human T-Cell Leukemia Virus Type 1 in Patients with Rare Bleeding Disorders

M. Naderi (PhD)[1], M. Narooie-Nejad (PhD)[1], Gh. Soleimani (MD)[2], F. Okati (MD)[3], H. Mahmoodi Nesheli (MD)[4], S. H. Soleimanzadeh Mousavi (MD)[5], S. Yaghoubi (MD)[*2]

1.Genetics of Non-Communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.
2.Children and Adolescents Health Research Center, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.
3.Department of Internal Medicine, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.
4.Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran.
5.Department of Pediatrics, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.

Article Type

Research Paper

Received:
Jan 25th 2021
Revised:
Apr 6th 2021
Accepted:
Jul 17th 2021

ABSTRACT

Background and Objective: Human T-cell leukemia virus type 1 (HTLV-1) is a virus that is endemic in some parts of the world, and as a pathogen, it can lead to severe infections in humans. Since no antiviral treatment is currently available and the only way of confrontation is prevention and identification of infected blood, this study was performed to determine the frequency of antibodies against HTLV-1 in patients with rare bleeding disorders receiving blood in Zahedan.

Methods: The study population included 180 patients with rare bleeding disorders referred to Ali Asghar Hospital in Zahedan selected by census method and 90 healthy individuals who referred to hospital lab selected by convenience sampling method in 2020. Age range was 1 to 39 years. Blood samples were collected from all participants and antibody test against HTLV-1 was confirmed using ELISA kit and positive ELISA test was confirmed using Real-time PCR.

Findings: In the case group, there were 86 men (47.8%) and 94 women (52.2%) and in the control group there were 43 men (47.8%) and 47 women (52.2%). Antibodies against HTLV-1 were found in 2 patients (1.1%) with rare bleeding disorders and none in healthy individuals. The first was a 29-year-old man with Glanzmann's disease who had severe Glanzmann's thrombasthenia. The second case was a 23-year-old woman with severe forms of factor V and factor VIII deficiency whose family history of Rare Bleeding Disorders (RBD) was positive.

Conclusion: The results of the study showed that the risk of HTLV-1 transmission through plasma-induced blood products and new types of coagulation factors seems negligible.

Keywords: *Rare Bleeding Disorders, Patients, Human T-Cell Leukemia Virus Type 1.*

Cite this article: Naderi M, Narooie-Nejad M, Soleimani Gh, Okati F, Mahmoodi Nesheli H, Soleimanzadeh Mousavi SH, et al. Frequency of Human T-Cell Leukemia Virus Type 1 in Patients with Rare Bleeding Disorders. *Journal of Babol University of Medical Sciences*. 2022; 24(1): 10-7.

***Corresponding Author: S. Yaghoubi (MD)**
Address: Ali-Ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, I.R.Iran.
Tel: +98 (54) 33295570. **E-mail:** yaghoubimd@yahoo.com

Introduction

Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus subtype of oncoviruses was first discovered in 1980 as a pathogen that can lead to severe human infection (1, 2). HTLV-1 is found natively in many areas including southwestern Japan, sub-Saharan Africa, South America, the Caribbean, and Australia-Malaysia (3-6). In Iran, it is also known to be native to Khorasan province, especially in Mashhad, Neishabour, and Sabzevar, with an estimated incidence of 2-4 cases per 100 (7). This virus is one of the few viruses that is not transmitted through free virus particles and is transmitted from an infected person, such as blood transfusions, cupping surgeries, the use of shared syringes, dental procedures, breastfeeding, and sexual contact (8). Because no specific antiviral treatment is available against HTLV-1 infection, the only way to prevent it is by determining the serum-positive and eliminating contaminated blood (9). Rare bleeding disorders account for about 3 to 5% of all congenital anomalies of coagulation factors (10, 11).

Due to the fact that rare bleeding disorders are relatively common in Sistan and Baluchistan province, and since blood products such as Fresh Frozen Plasma (FFP), platelets and cryoprecipitate (cryo) are used in the treatment of these patients and may be infected with HTLV-1 virus, the possibility of infection with this virus is increased by repeated injections of products in these patients. Therefore, this study was performed to determine the frequency of HTLV-1 virus infection in patients with rare bleeding disorders and compare it with the rate of infection with this virus in healthy individuals.

Methods

After approval in the ethics committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1392.6217, this case-control study was performed on all patients with rare bleeding disorders who referred to Ali Asghar Hospital in Zahedan in 2020 to receive blood products. The sample size included 180 patients and also 90 healthy individuals of the same gender and age as the case group and selected among those who referred to the laboratory of Ali Asghar Hospital and had no history of blood transfusion or surgery. After obtaining informed consent from eligible individuals for the project, they entered the study.

Patients' data including age, gender, type of bleeding disease, disease severity, product consumed and duration of receiving the product were extracted from patients' medical files and recorded in information forms. Then, 3 cc of blood samples were taken from all the subjects and kept in the freezer at a temperature of minus 20 °C until the test. After collecting all the samples and preparing a special kit (ITALY HTLV1 & 2 Ab version ULTRA), ELISA test for anti-virus antibodies was performed. Then, 3 cc of whole blood sample in tubes containing EDTA anticoagulants was obtained again from positive ELISA cases to confirm HTLV-1 infection and real time PCR test was performed. Finally, the data were analyzed using SPSS software and T-test and chi square statistical tests and $p<0.05$ was considered significant.

Results

In two cases (1.1%) out of 180 patients, there was virus infection and was not observed in any of the healthy individuals. There was no significant difference between the two groups in terms of virus infection. The most common type of product consumed among patients was FFP in 115 patients (63.8%) and the least common type of product was platelets in 15 patients (8.3%). Virus infection was observed in one patient

receiving platelets and one patient receiving FFP. Most patients with factor XIII deficiency used 72 units of Fibrogammin (about 6 years before the product became available on a monthly basis) and one unit of blood, and used more FFP before availability of Fibrogammin. The lowest FFP use among patients was 3 units in a 2-year-old girl and the highest was 170 units in a 23-year-old woman. The highest rate of cryoprecipitate used was 180 in an 11-year-old girl with a severe form of the Von Willebrand disease (VWD) and the lowest rate was 2 units in a 25-year-old woman with a mild form of the disease. Patients with von Willebrand also had a history of one to eight units of blood transfusions (37 in total).

Patients with Glanzmann thrombocytopenia were treated with platelets, with a minimum of 13 units in a 20-year-old man and a maximum of 150 units in a 29-year-old woman. They also had a history of 4 to 15 units of blood (98 units in total). One of the two cases infected with HTLV-1 in this study was among those patients who received 43 units of platelets and five units of blood. There were fifteen patients with factor V deficiency in this study, the youngest, a 5-year-old girl and the oldest, a 36-year-old woman, who received 11 and 120 units of FFP and received 1 and 2 units of blood, respectively, and the third case suffered from severe form of disease. The second person positive for HTLV-1 infection was among the patients receiving FFP. Other patients included three patients with factor I deficiency (a 26-year-old man receiving 13 units of cryo and two units of blood, a 22-year-old man receiving 13 units of cryo and one unit of blood transfusions, an 18-year-old man receiving 8 units of cryo), three patient with combined factor V and VIII deficiency (a 19-year-old man receiving 18 units of FFP and two units of blood, a 23-year-old woman receiving 19 units of FFP and three units of blood, a 20-year-old man receiving 14 units of FFP and one unit of blood) and three patients with Bernard-Soulier syndrome (a five-year-old girl receiving 15 units of platelets and one unit of blood, a 4-year-old girl receiving 14 units of platelets, a 3-year-old girl receiving 10 units of platelets and one unit of blood). The total amount of FFP consumed in the case group was 4702 units (average of 35 units per patient), 3226 units of platelets (average of 17 units per patient), 378 packed cells, 6265 units of Fibrogammin and 1204 units of cryo.

In the case group, there were 86 men (47.8%) and 94 women (52.2%) and in the control group, there were 43 men (47.8%) and 47 women (52.2%). In the case group, the maximum and minimum ages were 39 and 1, respectively. The mean age of people in this group was 14.5±11.2 years. In the control group, the maximum and minimum ages of individuals were 35 and 1, respectively, and the mean age of individuals in this group was 15.7±10.6 years. Most subjects of both groups were in the age range of 16 to 30 years and a few of them were in the age range of more than 30 years. 39.5% of subjects in the case group and 21.2% of subjects in the control group were illiterate. The rate of university education in the control group was 22.2% and in the case group was 5%. HTLV-1 infection was found in two cases of severe RBD. One positive case was a 29-year-old man from Khash County with severe Glanzmann thrombocytopenia and a positive family history of RBD. This person did not have a history of traveling to Khorasan province and blood transfusion in this province. This patient has been treated with 43 units of platelets for 26 years and also had a history of receiving 5 blood transfusions. The second case was a 23-year-old woman from Zahedan who suffered from severe forms of factor V and VIII deficiency and had a positive family history of RBD. This patient has been treated with FFP (19 units) for 15 years and also has a history of receiving 3 blood transfusions. One hundred and sixty-five patients (91.6%) had a severe form of the disease and a mild form of the disease was observed in nine patients (5%). The rest of the patients (3.4%) were classified in moderate category of disease. Two patients with a history of 26 years and 15 years receiving blood products were infected with the virus. The shortest duration of the product among patients was one year in a one-year-old infant with factor XIII deficiency, and the longest was 27 years in a 29-year-old woman with Glanzmann disease. The average duration of receiving product in each patient was 8.5±7.35 years. Among patients, 128 had factor XIII deficiency (71.2%), 15 had von Willebrand disease (8.4%), 12 had Glanzmann

thrombocytopenia (6.6%) and 15 had factor V deficiency (8.4), 4 had factor I deficiency (2.2), 3 had combined factor V and VIII deficiency (1.6%), and 3 had Bernard-Soulier syndrome (1.6%). In more than half of the subjects in the case group (61.5%), there was a family history of rare bleeding disorders, while in none of the subjects in control group, there was a family history in this regard. In the case group, the majority of people were from southern part of the province, while in the control group, almost half of the people were from this region. In the case group, about 12% of people were from northern region, while in the control group, this rate was about 30%. All were negative in terms of hepatitis C and there was only one positive case for hepatitis B, which was a 13-year-old boy with severe factor XIII deficiency (Table 1).

Table 1. Distribution of relative frequency of participants in the study according to the examined variables

Variable	Study group	Control group
	Number(%)	Number(%)
Gender		
Male	86(47.8)	43(47.8)
Female	94(52.2)	47(52.2)
Age (years)		
0-5	35(19.4)	13(14.4)
6-10	31(17.2)	19(21.1)
11-15	30(16.7)	14(15.6)
16-30	62(34.5)	38(42.2)
>30	22(12.2)	6(6.7)
Education status		
Illiterate	71(39.5)	19(21.2)
Elementary school	58(32.3)	20(22.2)
Middle school	21(11.6)	22(24.4)
High school	21(11.6)	9(10)
University	9(5)	20(22.2)
Illness severity		
Mild	9(5)	-
Moderate	6(3.4)	
Severe	165(91.6)	
Product receiving time (years)		
1-5	84(46.7)	
6-10	54(30)	
11-15	19(10.5)	-
16-20	11(6.1)	
21-25	8(4.5)	
26-30	4(2.2)	
Type of RBD disease		
Factor I deficiency	4(2.2)	
Factor V deficiency	15(8.4)	
Factor V & VIII deficiency	3(1.6)	
Factor XIII deficiency	128(71.2)	-
VWD	5(8.4)	
Glanzmann	12(6.6)	
Bernard-Soulier	3(1.6)	
Family history		
Positive	132(73.3)	-
Negative	48(26.7)	
Geographical distribution		
North of province	125(69.5)	-
Center of province	29(16.1)	
South of province	26(14.4)	

Discussion

Our results showed that two people in the case group (1.1%) had antibodies against HTLV-1, but antibodies against HTLV-1 were not observed in any subject of the control group. There was no significant difference in terms of HTLV-1 infection between case and control groups. Comparison of patients in terms of disease type, disease severity, type of product used, amount of blood or product usage and duration of product reception showed no association with infection and no significant difference was found. Another factor examined in this study is family history of rare bleeding disorder. The results of our study confirm the hereditary nature of the disease and the two infected subjects in this study had a positive family history; two sisters and a brother had the same disease. However, their test was negative for virus infection, so there was no association between family history of the disease and infection with the virus. Another criterion in the two groups was place of birth, and it was observed that the majority of subjects in the case group was from the northern cities of the province and in the control group no significant difference was found, indicating a higher prevalence of rare bleeding disease in the northern region. In terms of the product consumed, one person receiving FFP and one receiving platelet had a viral infection.

HTLV-1 virus is spread all over the world according to various studies, including the south of Japan, the Caribbean in the south of the United States and areas in South America and Africa, as well as in Iran, especially in the city of Mashhad and northeast of Iran, which is endemic to this virus (3-7, 12, 13). In a study on 16,000 blood donors in 21 blood transfusion centers in the country, the overall prevalence was 29%, 97.1% in Mashhad and from 0 to 0.5% in other cities (14-16). Studies by Shoeibi et al. and Rezaee et al. showed that a large number of HAM/TSP patients became infected with the HTLV-1 virus after receiving blood (17, 18), but Iranian patients are much less likely to get the disease compared to the Japanese and Brazilian populations. This difference may be due to genetic issues, environmental factors and different lifestyles of the two groups.

In the control group of our study, the prevalence of infection was zero percent, which is almost similar to some studies in Germany, Greece and Ilam. Due to its low rate compared to some studies, it can be due to different geographical prevalence of the virus (which depends on several factors, including environmental, socio-behavioral and health factors of residents), different laboratory methods, differences in the choice of study population (inclusion criteria and the objective of the study). The number of thalassemia and hemodialysis patients in Mazandaran in 2013 was 1.4 and 0.6% respectively, hemophilia patients in Birjand in 2007 was 1.2%, hemodialysis patients in Urmia in 2008 was 1.05%, in thalassemia patients in Zabol and Zahedan in 2001 was 1.6%, thalassemia patients in Italy in 1992 was 23%, hemodialysis patients in Paris in 1992 was 1.4%, and hemodialysis patients in Japan in 1989 was 33.8% (19).

As can be seen, the results of some studies such as the ones in Birjand, Mazandaran, Zabol, Zahedan, Urmia and Paris are similar to our study group and in some other studies, the level of infection is higher, which is also true for healthy people in the case group. In addition, it should be noted that most studies with a higher rate of infection have been related to thalassemia patients, from which it can be concluded that the risk of transmitting HTLV-1 virus through plasma-derived products (FFP), which is the most widely used product among hemophilia patients, is low, and the risk is higher in blood cell products such as PC, which is used in thalassemia patients.

Although the patients treated with blood products had a history of multiple injections, they did not differ significantly from healthy individuals in terms of HTLV-1 infection. However, the risk of transmission of HTLV-1 through plasma-derived blood products and new coagulation factors are very low and close to zero. Studies in a wider range of patients and healthy individuals are recommended.

Funding: This study was not supported by any organization.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Acknowledgment

We would like to thank the departments of Hematology, Hemovigilance and Bleeding Diseases of Ali Asghar (AS) Hospital in Zahedan for their cooperation with this study, as well as the participants of this study.

References

1. Fuzii HT, da Silva Dias GA, de Barros RJ, Falcão LF, Quaresma JA. Immunopathogenesis of HTLV-1-assoaciated myelopathy/tropical spastic paraparesis (HAM/TSP). Life Sci. 2014;104(1-2):9-14.
2. Soltani A, Hashemy SI, Zahedi Avval F, Soleimani A, Rafatpanah H, Rezaee SA, et al. Molecular targeting for treatment of human T-lymphotropic virus type 1 infection. Biomed Pharmacother. 2019;109:770-8.
3. Bartholomew C, Saxinger WC, Clark JW, Gail M, Dudgeon A, Mahabir B, et al. Transmission of HTLV-I and HIV among homosexual men in Trinidad. JAMA 1987;257(19):2604-8.
4. Cantor KP, Weiss SH, Goedert JJ, Battjes RJ. HTLV-I/II Seroprevalence and HIV/HTLV coinfection among U.S. intravenous drug users. J Acquir Immune Defic Syndr (1988). 1991;4(5):460-7.
5. Fukushima Y, Takahashi H, Hall WW, Nakasone T, Nakata S, Song P, et al. Extraordinary high rate of HTLV type II seropositivity in intravenous drug abusers in south Vietnam. AIDS Res Hum Retroviruses. 1995;11(5):637-45.
6. Hisada M, Chatterjee N, Zhang M, Battjes RJ, Goedert JJ. Increased hepatitis C virus load among injection drug users infected with human immunodeficiency virus and human T lymphotropic virus type II. J Infect Dis. 2003;188(6):891-7.
7. Akbarin MM, Rahimi H, Hassannia T, Shoja Razavi G, Sabet F, Shirdel A. Comparison of HTLV-I Proviral Load in Adult T Cell Leukemia/Lymphoma (ATL), HTLV-I-Associated Myelopathy (HAM-TSP) and Healthy Carriers. Iran J Basic Med Sci. 2013;16(3):208-12.
8. Farre L, de Oliveira Mde F, Primo J, Vandamme A-M, Van Weyenbergh J, Bittencourt AL. Early sequential development of infective dermatitis, human T cell lymphotropic virus type 1-associated myelopathy, and adult T cell leukemia/lymphoma. Clin Infect Dis. 2008;46(3):440-2.
9. Gonçalves DU, Proietti FA, Ribas JG, Araújo MG, Pinheiro SR, Guedes AC, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 2010;23(3):577-89.
10. Soleimani G, Shafighi Shahri E, Shafighi Shahri E. Liver function tests abnormality in influenza H1N1 in Southeastern of Iran. Biomed Res-India. 2017;28(3):1050-3.
11. Soleimani G, Sadeghi Bojd S, Tajik M, Shafighi Shahri E, Rashidi S. Paraclinical evolutions regarding liver and renal abnormalities of Kawasaki disease in the Southeast of Iran. J Compr Ped. 2014;5(1):e15777.
12. Mozhgani S-H, Zarei-Ghobadi M, Teymoori-Rad M, Mokhtari-Azad T, Mirzaie M, Sheikhi M, et al. Human T-lymphotropic virus 1 (HTLV-1) pathogenesis: A systems virology study. J Cell Biochem. 2018;119(5):3968-3979.
13. Naderi M, Eshghi P, Saneei Moghaddam E, Alizadeh Sh, Dorgalaleh A, Younesi MR, et al. Safety of human blood products in rare bleeding disorders in southeast of Iran. Haemophilia. 2012;19(2):e90-e2.
14. Sadeghipour A, Khodadad K, Kumar, PV, Nikougoftar M, Aghili, N. The first report of familial adult T-cell leukemia/lymphoa in Iran. Turk J Cancer. 2005;35(3):136-7.
15. Poukarim M R, Khamisipour G, Zandi K, Roustaee M H. Prevalence of anti-HTLV-I & anti-HTLV-II antibodies in Blood donors in Bushehr Province. Iran South Med J. 2004;6(2):161-4. [In Persian]
16. Azami M, Badfar G, Esmaeli E, Moslemirad M, Rahmati S. Epidemiology of human T-lymphotropic virus type 1 among blood donors and general population in Iran: a meta-analysis. Future Virol. 2018;13(8):585-99.
17. Shoeibi A, Rafatpanah H, Azarpazhooh A, Mokhber N, Hedayati-Moghaddam MR, Amiri A, et al. Clinical features of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in northeast Iran. ActaNeurol Belg. 2013;113(4):427-33.
18. Vakili R, Sabet F, Aahmadi S, Boostani R, Rafatpanah H, Shamsian S, et al. Human T-lymphotropic virus type I (HTLV-I) proviral load and clinical features in Iranian HAM/TSP patients: comparison of HTLV-I proviral load in HAM/TSP patients. Iran J Basic Med Sci. 2013;16(3):268-72.

19.Ghafari J, Yazdani Cherati J, Haghshenas MR. Prevalence of Human T-lymphotropic Virus in patients with Multiple Transfusions (Thalassemia, Hemophilia and Hemodialysis). J Babol Univ Med Sci. 2015;17(5):44-51. [In Persian]