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HTLV-1: ancient virus, new challenges

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ABSTRACT

Human T-lymphotropic virus (HTLV-1) is an ancient pathogen for human being but arising and recognized recently. The routes of transmission are vertical (mainly by breastfeeding), unsafe sexual contacts and through contaminated blood components specially in whom need frequent and repeated blood transfusions such as permanent anemia due to blood loss in hemophilia and major thalassemia. Patients who should undergo hemodialysis in their lifelong are another instance for increased risk of HTLV-1 exposure. The main HTLV-1-associated diseases are tropical spastic tetraparesis (HAM/TSP), an inflammatory myelopathy and adult T-cell leukemia (ATL). Although HTLV-1 is scattered around the world, only in endemic areas where prevalence rate is more than 1%, viral burden of infection have accumulated. Japan, Southern and Central parts of Africa, Caribbean basin and Iran are examples of endemic areas of HTLV-1. In this article, a rapid and brief review of HTLV-1 virology, immunology and pathogenesis have emerged. In addition, a short debate has driven about current statues of HTLV-1 in Iran.

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Introduction

The human T-lymphotropic virus (HTLV-1) was recognized about 30 years ago in a case of adult T-cell leukemia for the first time. This isolated virus confirms the hypothesis that human retroviruses can participate as a contributor for developing cancer (1,2). About 10 to 20 million people are infected with HTLV-1 around the world

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(3). A vast majority of infected individuals remain asymptomatic but about 3-5% of them display diseases due to this virus. These disorders include malignancies such as adult T-cell leukemia and lymphoma, inflammatory diseases such as myelopathy/ tropical spastic paraparesis (HAM/TSP) and opportunistic infections such as Strongyloides stercoralis (4,5). The critical pathogenesis of these diseases is pertained to lymphocytic dysfunction infected by HTLV-1. It is remarkable that these disorders do not appear in majority of carriers, which is probably due to influence of other factors other than etiological role of HTLV-1 (6).

HTLV-1, a type C virus, is a member of Deltaretrovirus genus in Retroviridae family. Other members of this oncovirus family include HTLV-2, bovine leukemia virus (BLV), simian T-cell leukemia (STLV), HTLV-3 and HTLV-4 (7).

The main structure of virus consists of a double layer proteolipid membrane. Enveloping inner contains include capsids, reverse transcriptase, polymerase and other protease enzymes. The main virion, consisting of a single strand RNA, is surrounded by an icosahedral capsid. The viral diameter is about 100 nm (8).

To capture the entire human cell as a host, viral genome should insert to host cell DNA. This purpose is achieved when single strand RNA converts to double strand DNA and then arrives to host genome DNA. This arrival viral DNA is called provirus (2). All retroviruses produce permanent infection including HTLV-1. The same as HIV, the most interested cell for HTLV-1 is $CD4^+$ T cell, but $CD8^+$ T cells also could be selected as alternative host cell.

HTLV-1 has a double genetic structure, encompasses of two similar strands with a length of 9032 base pairs for each one. The genomic structure, similar to other retroviruses, contains of two ending long terminal repeat (LTR) series in both side named gag, pol and env genes (2,8). In addition, HTLV-1 has particular segment namely pX between env and 3`LTR, responsible for encoding of regulatory important proteins such as p40 tax (TAX), p27rex, p12, p13 and p30. Moreover, pX region is responsible for encoding of HTLV-1 basic leucine zipper factor (HBZ), a gene that is involved in pathogenesis of virus (9).

Spreading of HTLV-1, in contrast to HIV, occurs directly through cell to cell contact rather than free plasma a particle, resulted in low and undetectable plasma virus. Further way for spreading is transmission from dendritic cells to $CD4^+$ T cell. In this way, infection of both dendritic and T cells perform by means of glucose transporter that plays as a receptor for HTLV-1 envelope glycoprotein (10-13). After arriving at host cell, RNA strand undergo a reverse transcription to produce double strand DNA named provirus to insert it to host DNA randomly. After insertion whenever a mitotic division occurs for host cell, HTLV-1 genome replication occurs. By this way, HTLV-1 replication is completely dependent on host cell and not viral DNA polymerase, a way in which viral genome transcription is guaranteed accurately and causes high stability for HTLV-1 genome (14). When provirus is installed in host genome, permanent infection of cell establishes and the host cell undergoes a plenty of changes under influence of viral production. These changes are not harmful for host cell. Whether the infected person become a healthy appearance carrier or a severe case of spastic tetraparesis is partially dependent to the degree of peripheral blood mononuclear cells (PBMCs) loading of provirus. Loading of 0.1 to 1% causes only a healthy carrier and loading rates up to 30% results in a HAM/TSP victim (15). Proviral loading is not correlated with sex or age but

varies with duration of infection (16). Host factors including MHC class 1 variations and subsequent antigen presentation to CD8 T cells are more important for determination of proviral loading rather than HTLV-1 (17, 18). In opposite to HIV-1, HTLV-1 causes a low number of viruses in plasma due to lower rate of viral replication but with high loyalty in replication which results in high stability for HTLV-1 (19). Furthermore, HTLV-1 not only does not cause host cell death, but also it facilitates cell proliferation and transformation (20). ALT and HAM/TSP that caused by HTLV-1 are different in pathogenesis and route of transmission. ALT is a malignant disorder of T cells transmitted via breastfeeding while HAM/TSP, which has an inflammatory foundation, is broadcast through blood transfusion. HTLV-1 can result in cellular transformation followed by ontogenetic alterations by means of viral products, which interact with host proteins mainly transcription factors and deviates their functions. The most critical molecule for pathogenesis of HTLV-1 and cell transformation is TAX, a phosphoprotein with 40 Kda weight (21-24).

Immunologic response to HTLV-1 is displayed in both cellular and humoral levels. Antibodies to gag, env and tax are manufactured in order of time respectively (25). TAX antibody seems to play an important role in HAM/TSP pathogenesis and there is a linear relation between higher TAX antibody and elevated proviral load and subsequently developing HAM/TSP (26). In cellular level, HTLV-specific cytotoxic T-lymphocytes (CTLs), which are found both in carriers and in associated-HTLV-1 ALT and HAM/TSP diseases, is essentially stimulated by TAX protein epitopes (27,28). It has been assumed that tha virus is able to escape from CTL killing duty by mutation in its TAX (29). Malfunction of CTLs in both diseases have been described (30-32).

The most common way of HTLV-1 transmission is breastfeeding followed by blood transfusion, needle sharing and high risk sexual behaviors. Vertical transmission causes clustering spreading of disease in defined geographical areas and special familial groups. HTLV-1 is endemic in many areas of the world including Southern Japan, Caribbean, South America, and Middle East, Southern and Central parts of Africa. HTLV-1 prevalence is under 1% in non-endemic areas and ranges from 5% to more than 30% in endemic sites. Parallel to increased age, the prevalence increases as well especially in women, with twice as likely to be infected as men, probably due to ability for sexual transmission from men to women (33).

There is a low variability in viral genome among patients and even among viruses founded in diverse geographical areas (14). Higher common similarity in HLA class 1 type between mother and child increases the likelihood of vertical transmission (34).

The prevalence estimation of HTLV-1 is essentially according to seropositivity of volunteer of blood donation and particular population groups such as pregnant women, IV drug abusers, patients who need frequent blood transfusions such as hemophilia, thalassemia and patients who need hemodialysis. Different diagnostic tests and variable criteria for test result interpretation causes significant variation in estimation of HTLV-1 prevalence between different studies. A worldwide spreading of HTLV-1 is assumed to originate from Africa, where phylogenetic studies have approved its central parts as the cradle of all different primate T-lymphotrophic viruses including HTLV-1 (35, 36). It is assumed that broadcasting of these primitive viruses has happened 27300 years ago and derivation of HTLV-1 has occurred 21100 to 5300 years ago (37). The scattering of HTLV-1 in Asia

is focused on Japan with more than 10% prevalence of general population in some areas of its southern parts (38,39) and Iran, Fujian, Taiwan and some parts of Chine with prevalence of 0.1% to 10% (40-42).

Current status of HTLV-1 in Iran

Eastern North of Iran is known as an endemic area for HTLV-1 since 1996 (43). Many studies have conducted to evaluate the HTLV-1 prevalence in general and in selected groups of population by different authors. Mashhad, Sabzevar and Neyshabour are studied for evaluation of HTLV-1 prevalence. In the first study published in 1996, Safai et al. reported 3% prevalence for HTLV-1 in Mashhad city in a population size of 696 people (13 subjects of lymphoma) (43). In the second study driven in 1999, the prevalence rate was 0.77% among 28926 healthy blood donors (42). Another study, in 2009 (published in 2011), confirmed Mashhad as an endemic area for HTLV-1 with a prevalence rate of 2.12% (44). Variability in the obtained results in these studies may be in part correlated with different applied diagnostic tests.

Sabzevar and Neyshabour, two other cities in Khorasan Razavi province neighbor to Mashhad, were studied for evaluating of HTLV-1 prevalence. Reported results in 2010 and 2012 showed 7.2% and 1.66% prevalence rate of HTLV-1 for Neyshabour and Sabzevar, respectively (45,46). The important parameters of these studies are presented in Table 1.

Among demographic characters, the role of age and sex seems to be more important

Table 1. HTLV-1 prevalence in endemic regions of Iran

Author Reference	City	Year	Study design	Number of participants	Screening test	Confirming test	Total prevalence %	Comment
Safai (43)	Mashhad	1996	—	707	PA*	WB	3	HTLV-1 subtype in Mashhad is the same as cosmopolitan subtype
Abbaszadegan (42)	Mashhad	2003	—	28926	ELISA**	WB	0.77	Regarding to HTLV-1 prevalence in other countries (USA: 0.004%, France: 0.004%, and Brazil: 0.42%) Mashhad remain an endemic area for HTLV-1.
Abedi (50)	Mashhad	2004-2005	Cross sectional study	126	Not given	Not given	Not given	HTLV-1 was more common in men than women.
Rafatpanah (44)	Mashhad	2011	Random cross sectional study	1678	ELISA	WB*** and PCR****	2.12	No difference was demonstrated between men and women HTLV-1 prevalence. Age had a significant association
Hedayati-Moghadam (45)	Neyshabour	2010	Non random sampling in a cross-sectional descriptive analytic study.	483	ELISA	WB	7.2	Prevalence rate had significant relation with age (the most important), family size,income and blood transfusion.
Azarpazhooh (46)	Sabzevar	2012	Cross sectional study	1445	ELISA	PCR	1.66	Prevalence increased with age>30 yr and positive history of surgery, imprisonment and hospitalization.

*PA: Gelatin particle agglutination; **ELISA: Enzyme-linked immunosorbent assay;*** WB: Western blot; ****PCR: Polymerase chain reaction.

in these studies.

According to Abedi et al. survey, the most important risk factor for HTLV-1 infection was medical injection medication such as dental procedure (85.7%) in Iran, followed by tattoo (10.1%), unsafe sexual behavior (7.9%) and transfusion of blood products (8.7%) (47). Repeated need to blood component transfusion put the patients in exposure of elevated risk to be infected by blood borne pathogens including HTLV-1 including hematologic patients and end-stage kidney disease patients that experience frequent hemodialysis in his or her lifelong. Increased risk groups such as patients with hemophilia, major thalassemia and hemodialysis-undergoing patients have been investigated for HTLV-1 prevalence in Iran. The characters of these studies are showed in Table 2.

As HTLV-1 displays an intracellular function necessarily, it seems cell-free

Table 2. HTLV-1 prevalence in high risk populations in Iran

Author/ year/ Reference	**City or province**	**Sampling and number of participants**				**Positive by ELISA (%)**	**Confirmed positive samples**	**Comment**
		Healthy blood donor	***Hemophilia***	***Thalassemia***	***Hemodialysis dependent***			
Abedi 2007-2008 (51,52)	Hormozgan	1100	7	163	40	5/163 (3.06%) 5/1100 (0.18)	5/5 5/5	Probably infected patients are resulted of unsafe blood transfusions
Karimi 2007 (53)	Chaharmahal-bakhtiari	800	0	357	___	27/357 (7.6%) 5/800 (0.62)	24/27 5/5	The authors concluded that HTLV-1 prevalence estimation is near to endemic areas.
Khamene 2008 (54)	Urmia	206495	0	0	___	(0.34%)		HTLV-1prevalence is as high as endemic areas.
Ghadiri 2010 (55)	Kermanshah	10000	0	116	___	4/116 (3.4%) 5/1000 (0.5%)	4/4 5/5	Infection exist in the area
Mortezai 2011 (56)	Isfahan	1400	0	150	___	5/150 (3.3%) 0/140	5/5	No significant association with gender
Ghaffari 2013 (57)	Mazandaran	0	0	288	___	20/288 (0.07%)	20/20	HTLV-1 prevalence in hemodialysis patients was not as high as other regions.
Ghaffari 2013 (58)	Sari and Ghaemshahr	00	160	0	___	1/160 (0.6%)	1/1	HTLV-1 risk is low in this region and no need to blood screening.

blood products such as cryoprecipitate, fresh frozen plasma and coagulation factor concentrates remain intact and safe in blood transfusion (48,49).

Conclusion

HTLV-1 as a worldwide health problem has not recognized sufficiently up till now. There are no essential treatment for its main associated disorders except for symptomatic relief management and the lack of a substitute marker to follow up remains a challenge for clinical practitioners. Chronicity inherence of HTLV-1 infection in association with asymptomatic carriers who consist the majority of patients contribute to silent spreading of infection, particularly in frequent implication with blood transfusion, make its control hard if not impossible. Although there is not a precise drug to treat, meticulous blood screening protocols and recognizing infected nursing mothers remain the fundamental prophylactic implementation to control broadcasting of infection.

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Conflict of Interest

The authors declare no conflict of interest.

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