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The Relevance of HTLV-1-associated Myelopathy/Tropical Spastic Paraparesis in Iran: A Review Study

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ABSTRACT

Human T-cell lymphotropic virus type I (HTLV-I) is a retrovirus, which is the causative agent of adult T-cell leukaemia (ATL) and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Evidence suggests that the interaction of HTLV-1 with the cellular-immune system plays a key role in the development of HAM/TSP. However, the main mechanism in this regard remains unknown. The present study aimed to review the HAM/TSP pathogenesis, current status of HTLV-1 in Iran, and available treatments for HTLV-1 infection.

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Introduction

There are four types of the human T-cell lymphotropic virus (HTLV), which is among the most important human pathogens, belonging to genus Deltaretrovirus, Retroviridae family, and Orthoretrovirinae subfamily. HTLV-1 is an enveloped virus consisting of two positive-sense, single-stranded RNA molecules. Its RNA consists of two cluster genes, including functional genes (e.g., gag, pro, pol, and env) and structural genes, which are classified as two long terminal repeat (LTR) regions. Interestingly, the pX region is located between the env gene and 3´ LTR region (Figure 1). The gag gene encodes p15, p19, and p25 structural proteins, the pol gene encodes two main enzymes (reverse transcriptase [RT] and integrase), the pro gene encodes protease, and the env gene encodes gp21 and gp46 glycoproteins. The pX region also contains regulatory genes, which encode regulating proteins, such as Tax (p40), REX (p27), p12, p13, p21, p30, and HTLV-1 bZIP factor (HBZ). These proteins play a pivotal role in the regulation of virus propagation, suppression of human p53 protein, and carcinogenicity (1).

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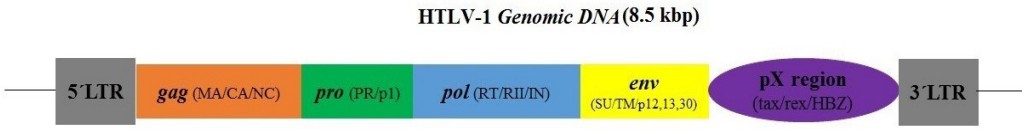

Figure 1. HTLV-1 Genome Map (HBZ: HTLV-1 bZIP-factor; LTR: long terminal repeat; MA: matrix; CA: capsid; NC: nucleocapsid; PR: Protease; RT: reverse transcriptase; IN: integrase; SU: surface subunit; TM: transmembrane region; Env: envelope glycoprotein)

Literature Review

In 1980, Poiesz et al. isolated and identified HTLV-1 in a 28-year-old black patient with T-cell lymphoma for the first time (2). Following that, the virus was introduced as the agent of T-cell leukemia (ATL) (first described in Japan in 1977) and associated with the neurological diseases, which were described by Gessian et al. in 1985.

In another study, a Martinican patient with tropical spastic paraparesis was reported to have high titers of anti-HTLV-1 antibodies. In 1988, the World Health Organization (WHO) introduced HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) as a disease (3,4). Approximately five million cases of infection with HTLV-1 have been reported worldwide, most of which are in endemic areas, such as the south of Japan, Caribbean basin, central and western Africa, the Middle East, Australia, Melanesia, Papua New Guinea, and central and south America (5).

HTLV-1 could be transmitted perinatally and through breastfeeding, sexual contact, injections, and blood transfusions (2-4). By the age of 40 years, nearly 5% of the infected patients are affected by life-threatening diseases, such as ATL, HAM/TSP, myositis, arthritis, alveolitis, dermatitis, uveitis, and HTLV-1 associated rheumatoid arthritis. Nevertheless, 95% of the infected patients remain asymptomatic throughout their lifetime (2,6).

According to recent data, approximately 0.25-3.8% of the patients with HTLV-1 infection are faced with the progression of the infection to HAM/TSP, which is a destructive, chronic inflammation of the spinal cord, especially in the mid and thoracic segments. Although HAM/TSP is often a complex and slowly-evolving process, the onset of inflammation and subsequent clinical symptoms are remarkably more rapid (less than two years) in 21.5% of the cases due to epigenetic changes (6,7).

HAM/TSP normally occurs in patients aged 40-50 years and is more prevalent in women compared to men (female-to-male ratio: 2:1) (8). The clinical symptoms of the infection include lower-extremity paralysis, pain, urinary incontinence, constipation, lethargy, and hyperflexion (2-5). With regard to HAM/TSP progression, some of the main risk factors include high viral titer, high titers of specific antibodies against HTLV-1, HLA class type I alleles (e.g., HLA-A, HLA-A02, HLA-Cw08, HLA-DRB1, and HLA-B7), single-nucleotide polymorphism in cytokine genes (e.g., IL-6-634C, IL-10-592A, and IL-28B), increased regulatory T cells, increased type I and II interferon, and increased expression of chemokine receptors and IP-10 (CXCL10) (5,9).

HAM/TSP develops in two stages; the first stage involves the migration and accumulation of lymphocytes on the spinal cord, and inflammatory metabolites (especially IFN-γ) are activated in the second stage, thereby causing atrophy, demyelination, and nerve cell destruction (2,7). With its ability to recognize various surface receptors, HTLV-1 could enter numerous immune cells, such as T CD4+, T CD8+ (CTL), regulatory T cells, B cells, dendritic cells (DCs), and macrophages (MΦ). These receptors consist of heparan sulfate proteoglycans, glucose transporter-1, neuropilin-1, CCR4, CXCL10, CXCR3, and VCAM-1 and VLA-4 integrins (9). However, the histopathological investigation of central nervous system samples has confirmed the pivotal roles of HTLV-1-specific CD8+ and CD4+ cells in HAM/TSP.

According to reports, the viral load from the blood samples of symptomatic patients is often significantly higher compared to asymptomatic carriers. Recent findings in this regard have demonstrated that in-vitro conditions could propagate HTLV-1-specific CD4+ cells, thereby leading to the excessive production of IFN-γ and IFN type I. It is also notable that Tax and HBZ proteins are responsible for such changes (3,10). Through the inhibition of p53, BCL1B, and TP53INP1 proteins, DNA repair system (attenuating the expression of Mad1), Akt pathway, TGF-β expression, and the activation and stimulation of reactive oxygen species, IFN-γ production, and NF-kB, the Tax protein causes a series of events, including cell proliferation, dissemination of viruses to adjacent cells, aneuploidy, and eventually nerve cell destruction (9,11). In addition, the HBZ protein plays a key role in the progression of HAM/TSP pathogenesis via concurrent events, stimulation of cytotoxic T cells (CTLs), E2F-1, T-bet production, inhibition of

PI3K and CREB2, reduction of Foxp3 expression, and affecting CycD1 (10,11).

According to the literature, the incidence of this destructive infection is predictable. Under the influence of TNF-α and viral Tax proteins, HTLV-1-infected Th1 cells produce and release high levels of matrix metalloproteinases, MMP-2, and MMP-9, which cause the attenuation and destruction of the blood-brain barrier. On the other hand, increased IFN-γ expression due to the Tax protein leads to the proliferation of astrocytes and increased secretion of their chemokines, especially CXCL10. Released chemokines are recognized by the CXCR3 receptors on the surface of T CD4+ and T CD8+ lymphocytes. Following that, T lymphocytes migrate to the spinal cord and accumulate. The following events are the dissemination of the virus to the adjacent lymphocytes, as well as the production of IFN-γ, interferon type I, reactive oxygen species, interleukins (e.g., IL-2, IL-9, IL-15, and IL-21) and granzymes, resulting in a chronic inflammatory process and neuronal destruction (both the cell body and myelinated axon) (Figure 2). Another consequence is the manifestation of nervous symptoms, such as urinary incontinence, muscle weakness, hyperflexion, Babinski reflex, skin conditions, back pain, lower-extremity paraesthesia, and Sjogren's syndrome (10,12).

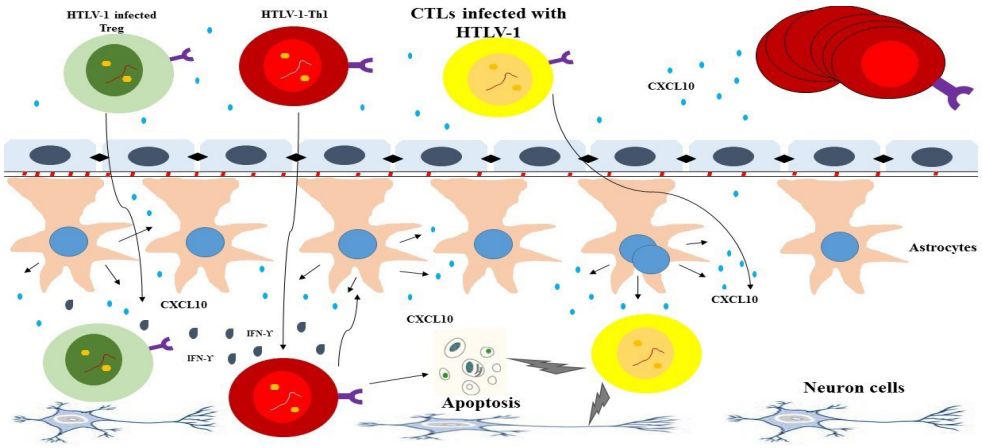

Figure 2. Schematic View of Various T Cell Types Infected with HTLV1- and Pathogenesis

In a research in this regard, Lezin et al. demonstrated that the rates of cerebrospinal fluid (CSF) cells and HTLV-1-infected T cells in the CSF of the patients with HAM/TSP were higher by 10% and 1% compared to asymptomatic carriers, respectively (13). Furthermore, laboratory studies have indicated that HTLV-1 virus prefers Th1 cells to other cells (e.g., regulatory T cells, macrophages, epithelial cells, and dendritic cells) despite its ability to infect many cell types (2-5).

In the later stages of inflammation, the virus infects CTLs in order to destroy nerve cells. In addition, the virus causes the formation of CCL2 chemokine via the expression of the Tax protein, which in turn is recognized by the CCR4 receptors on regulatory T cells as an appropriate reservoir for the virus. Recent findings have demonstrated that CD4+, CD25+, Foxp3+, and regulatory T cells express larger amounts of viral genomes compared to other cells. Today, it is clear that regulatory T cells are completely different during the course of infection since the Tax protein deteriorates the function of regulatory T cells as inflammation inhibitory cells through the reduction of the TGF-β and Foxp3+ factors. Therefore, HTLV-1 could use regulatory T cells as life-long reservoirs for its reproduction (5,10).

HTLV-1-associated infective dermatitis (ID) is common in the asymptomatic carriers living in endemic areas and considered to be a predictor of the development of ATL or HAM/TSP (14). Moreover, HTLV-1-associated cutaneous lesions are common in seropositive HTLV-1 asymptomatic carriers, as well as ATL and HAM/TSP patients. HTLV-1-associated ID is considered to be the primary sign of HTLV-1 infection in children (15,16). Crusted scabies and relapsing eczematous lesions are also prevalent in ATL and HAM/TSP. In this regard, Bittencourt et al. reported that 67% of Brazilian ATL patients had dermatological conditions (15,17).

In Iran, HTLV-1 is considered endemic in Khorasan provinces, especially in Mashhad, Neyshabour, and Sabzevar, with the incidence rate estimated at 2-4 cases per 100 (18). The first documented high prevalence rate of HTLV-1 was reported in 1983 from a lineage of Israeli immigrants born and living in Mashhad (19). According to previous reports, the prevalence of HTLV-1 in Iran was estimated at 2.49% during 2007-2018 (Table 1).

Furthermore, previous findings have denoted

Table 1. Prevalence of HTLV1- Infection in Iran (2018-2007)

Iran Provinces	Year of Study	Prevalence (%)	Subject
North Khorasan	2007	0.04	Healthy Subjects
	2009	0.05	Blood Donors
Razavi Khorasan	1996	2.6	Blood Donors
	1999	0.73	Blood Donors
	1997	0.82	Blood Donors
	2003	1.5	Blood Donors
	2004	0.45	Blood Donors
	2006	0.40	Blood Donors
	2007	0.39	Blood Donors
	2008	0.22	Blood Donors
	2008	0.36	Blood Donors
	2009	2.11	Blood Donors
	2009	7.2	Blood Donors
	2009	0.19	Blood Donors
	2009	0.25	Blood Donors
	2010	0.14	Blood Donors
	2010	0.26	Blood Donors
	2010	3.2	Healthy Subjects
	2011	0.11	Blood Donors
	2011	0.18	Blood Donors
	2011	1.25	Blood Donors
	2011	7.2	Healthy Subjects
	2012	1.47	Pregnant Women
	2012	1.47	Pregnant Women
	2012	1.6	Healthcare Workers
	2013	3.4	Healthy Subjects
	2014	0.1	Blood Donors
	2015	0.4	Blood Donors
	2015	0.1	Blood Donors
	2017	4.0	Thalassemic Patients
	2017	6.5	Thalassemic Patients
	2018	4	Sarcoidosis Patients
South Khorasan	2006	0.42	Healthy Subjects
	2008	0.29	Healthy Subjects
	2009	0.03	Blood Donors
Golestan	2007	7 .0	Blood Donors
	2009	0.29	Healthy Subjects
	2005	4.42	Healthy Subjects
	2013	0.29	Healthy Subjects
	2009	0.02	Blood Donors
Guilan	2016	20	Blood Donors
Mazandaran	2010	0.08	Healthy Subjects
	2013	0.6	Hemodialysis Patients
Tehran (capital of Iran	1996	4.59	Healthy Subjects
	2004	6.29	Healthy Subjects
	2011	0.4	Gastric Cancer Patients
	2011	33	Blood Cancer Patients
	2014	11	Thalassemic Patients
	2017	1.78	Blood Cancer Patients
Alborz	2009	0.05	Healthy Subjects
	2010	0.11	Healthy Subjects
East Azerbaijan	2009	0.01	Blood Donors
West Azerbaijan	2005	0.34	Blood Donors
	2006	1.05	Healthy Subjects
	2006	0.34	Healthy Subjects
	2009	0.06	Blood Donors
	2010	1.09	Renal Transplant Patients
	2016	0	Hemophiliacs
Ilam	2006	0.20	Blood Donors
	2010	0.002	Healthy Subjects
Fars	1994	2.5	Healthy Subjects
Chaharmahal and Bakhtiari	2006	6.72	Healthy Subjects
	2006	0.62	Healthy Subjects
Isfahan	2012	0.99	Leukemia Patients
Boushehr	2002	0.01	Blood Donors
	2003	2.18	Healthy Subjects
	2004	0.013	Healthy Subjects
Hormozgan	2007	0.18	Blood Donors
	2008	2.38	Healthy Subjects
	2008	0.18	Healthy Subjects
Sistan & Baluchestan	2002	1.6	Healthy Subjects
Kermanshah	2011	4	Thalassemic Patients
Other Provinces	No Study	Not Reported	Not Reported
Mean	2007-2018	2.49	

that several Iranian blood donors are infected with HTLV-1, which potentially leads to the expansion of the HTLV-1 virus in blood recipient populations. In Iran, HTLV-1 infection in blood products has not received sufficient attention, with the exception of Mashhad (20). In a study in this regard, Shoeibi et al. reported that a significant number of HAM/TSP patients had a history of blood transfusion during surgery or hospitalization (19). In addition, Rezaee et al. claimed that the HTLV-1

Table 2. Therapeutic Categories for Treatment of HAM/TSP Infection.

Drug	Example (dosage)	Main Mechanism
Corticosteroid	Prednisolone (1-2 mg/kg)	Inhibition and Suppression of Inflammation Process
Blood Purification	Plasmapheresis/lymphocytapheresis	Elimination of HTLV-1 Reservoir and IFN-γ, CD4+, and T cells
Pentoxifylline	Pentoxifylline (300 mg/day)	Immunomodulatory Activity for TNF-α and IFN-γ
Heparin	Heparin (5,000-10,000 units/day)	Inhibition of Lymphocyte Trafficking
Intravenous Gammaglobulin	IVIG (10 g/day or 400 mg/kg/day)	Binding to HTLV-1 Antigens
Vitamin C	Vitamin C (35-40 mg/kg/day)	Dysregulation of Mϕ
Interferon-α/β	IFN-α/IFN-β 3.0 MU	Imbalance of Th1/2, Dysregulation of Tax Expression, and Suppression of CD8+ T cell
Humanized Anti-Tac Antibody	Daclizumab (1 mg/kg)	Blockade of IL-2 Effects
Histone Deacetylase Enzyme Inhibitor	Valproate (20 mg/kg/day)	Inhibition of HTLV-1 Replication and Transcription
Prosultiamine	Prosultiamine	Similar to allicin, it has cytotoxic activity against HTLV-I-infected T cell lines.
Reverse-transcriptase Inhibitors	Zidovudine	Inhibition of HTLV-1 RT Activities
Protease Inhibitors	Indinavir	Inhibition of HTLV-1 PR Activities

proviral loads of Iranian HAM/TSP patients were lower compared to Japanese and Brazilian populations, and the difference in this regard was associated with the heterogeneity of host genomas, lifestyles, and environmental factors. Nevertheless, the neurological symptoms of HAM/TSP have been shown to be similar in these countries; such examples are stumble, urinary disorders, backache, constipation, and overall weakness (21).

Several methods are available for the screening of the presence of HTLV-1, including the ELISA assay, western blot (WB), and molecular-based techniques, each of which has some limitations. For instance, ELISA cross-reacts with HTLV-1 and HTLV-II, and false negativity is possible in WB in primary infection. However, the combination of ELISA and WB or molecular methods could reliably detect the cases with HTLV-1 (20,23).

No effective vaccination is available against HTLV-1, and chemotherapy is considered to be the only option for virus control. It is also notable that chemotherapy only decreases the viral replication cycle, and the infection reservoirs persist (6). Despite the lack of effective anti-HTLV-1 drugs (1,3,24), the therapeutic methods used for the treatment of HAM/TSP are divided into several categories, including glucocorticoids, histone deacetylase inhibitors, interferon alpha, vitamin C, blood purification, pentoxifylline, heparin, IV Ig therapy, anti-retroviral therapy, humanized anti-Tac, and prosultiamine. Many of these therapeutic regimens are in the clinical trial stage, while combination therapy has yielded favorable outcomes (Table 2) (3,5,25).

Conclusion

HTLV-1 is the first human retrovirus that causes severe complication, such as adult T-cell leuke-

mia/lymphoma (ATLL) and HAM/TSP. According to the literature, HTLV-1 proviral loads and various immune responses to HTLV-1 infections are the main cause of progression into ATL and HAM/TSP. In the present study, we discussed the immune-pathogenesis of HAM/TSP infection, and the findings suggested that CTLs and CD4+ T cell responses are responsible for establishing progressive inflammation in the spinal cord. In addition, microglial cells are influenced by the recruitment of the HTLV-1-infected T cells into the central nervous system using various chemokines, particularly CXCL10. Moreover, CD4+, CD2+, Foxp3, and regulatory T cells play a key role in determining the pathogenesis of HAM/TSP as the HTLV-1 reservoir cells suppressing the Th1 activities.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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