Journal of Advanced Biomedical Sciences

https://jabs.fums.ac.ir/

Online ISSN: 2783-1523

Fasa University of Medical Sciences

Neurological Manifestations and Risk Factors of HTLV-1 Infection in the Middle East Region and Iran: A Comprehensive Review of 137 Articles of the Last 23 Years

Ali Rajabpour-Sanati, Shahriar Irankhah, Laadan Rahmani, Hamid Reza Riasi

Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

Article Info

Article Type:

Review Article

Article history:

Received

05 Feb 2024

Received in revised form

21 Apr 2024

Accepted

31 Apr 2024

Published online

05 May 2024

Publisher

Fasa University of Medical Sciences

Abstract

Background & Objectives: The Human T-cell lymphotropic virus type 1 (HTLV-1) retrovirus is prevalent in some regions, such as Iran. This comprehensive literature review explores the symptoms and risk factors associated with HTLV-1 infection Middle East Region and Iran.

Materials & Methods: This narrative review used PubMed, Scopus, Embase, ScienceDirect, and Google Scholar as searching engines using terms HTLV-1, neurological disorders, pathogenesis, transmission, diagnosis, treatment, and epidemiology for articles published between 2000 and 2023. In total, 137 articles were eligible.

Results: Breastfeeding, unsafe sexual contact, and contaminated blood products are main HTLV-1 transmission routes. Brazil, Ecuador, and the Dominican Republic are countries with a high percentage of HTLV-1 infection, with estimates ranging from 1% to 13.9% in Brazil, up to 57% in Ecuador, and 1% to 5% in the Dominican Republic and it is endemic in Iran, Japan, the Caribbean, South America, and Africa. While numerous patients are asymptomatic, the virus can cause HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and peripheral neuropathy. Tax viral proteins cause nervous system inflammation and HAM/TSP. MRI (magnetic resonance imaging) may decipher spinal cord shrinkage and white matter lesions in affected patients. Immunodeficiency conditions, blood transfusion, and risky sexual behavior increase infection rate. The neurological symptoms are initiated with sensory-motor impairments. The main symptoms are limb weakness, bladder/bowel dysfunction, and cognitive impairment.

Conclusion: HTLV-1 infection is highly prevalent in Japan, Africa, the Caribbean, Central and South America, and Iran (especially in northeastern regions like Neyshabur). By understanding the pathogenesis and epidemiology of HTLV-1, proper strategies and targeted treatments can be developed for associated disorders like HAM/TSP. International collaboration is essential in addressing health concerns related to HTLV-1 infection.

Keywords: Human T-cell lymphotropic virus type 1, Epidemiology, Pathogenesis, Middle East

Cite this article: Rajabpour-Sanati A, Irankhah SH, Rahmani L, Riasi HR. Neurological Manifestations and Risk Factors of HTLV-1 Infection in the Middle East Region and Iran: A Comprehensive Review of 137 Articles of the Last 23 Years. J Adv Biomed Sci. 2024; 14(2): 77-93.

DOI: 10.18502/jabs.v14i2.15749

[DOI: 10.18502/jabs.v14i2.15749]

Introduction

Human T-cell Lymphotropic Virus type 1 (HTLV-1) is a retrovirus that infects a significant number of individuals globally.

Estimates suggest that between 5 to 20 million people worldwide are infected with HTLV-1, with prevalence reaching as high as 30% in certain regions

Corresponding Author: Ali Rajabpour-Sanati, F. 2, NO 16, Sepehr #8, Sepehr St, Faramarz Abbasi #25, Faramarz Abbasi Ave, Mashhad, Iran
Email: ali.poursanati@gmail.com

(1–5). Vertical transmission, particularly through breastfeeding, is a primary mode of spread contributing to clustered infection foci in specific geographical areas like Japan, the Caribbean, sub-Saharan Africa, the Middle East, South America, and indigenous communities in Australia (3). Women predominantly carry the burden of HTLV infection worldwide, often acquiring the virus through condomless sex and unknowingly transmitting it to their offspring (6).

The epidemiology of HTLV-1 is complex, with endemic foci in regions like Japan, the Caribbean, South America, Central Africa, and specific areas in Iran and Melanesia(1,5). Studies have highlighted the need for better understanding and efforts to reduce the prevalence of HTLV-1, given its association with severe diseases and the lack of reliable epidemiological data (2).

Based on the investigations conducted in various texts and articles from 2000 to 2023, it has been evident that the level of HTLV-1 virus contamination in Iran's Northern and Northeastern regions is consistently higher than in other areas. This level is also observed to be significantly elevated in other Middle Eastern countries (7), emphasizing the necessity of better understanding this virus and its transmission methods in this region. In the affected areas, most individuals are asymptomatic, but due to the virus's penetration into the nervous system, the disruption of the cellular defense system, and the release of inflammatory cytokines, individuals can develop neurological diseases, with the most prominent form being HTLV-1-Associated Myelopathy (HAM)/Tropical Spastic Paraparesis (TSP) (HAM/TSP). Half of HAM/TSP receiving follow-up care will become wheelchair-dependent, severely affecting their independence and quality of life (8). These individuals often experience atrophy in the motor nuclei of the brain, as well as disorders in the white matter of the brain and spinal cord (affecting the thoracic and cervical regions (9)), leading to extensive motor and sensory impairments and even autoimmune manifestations. Involvement can occur at the central or peripheral nervous system level, significantly affecting patients' functional and social aspects. Considering the pathogenesis of the virus, which leads to an abnormal increase in inflammatory cytokines in response to viral proteins, the reduction or elimination of cytokines can assist in alleviating patient symptoms. In this regard, drugs that modulate cytokines quantitatively and qualitatively can be employed.

Materials and Methods

This review study was conducted using data obtained from databases such as PubMed, Scopus, Embase, Science Direct, and Google Scholar. The retrieved results included those articles published between 2000 and 2023. The study was carried out as a narrative review, and involved no independent data resulting from direct clinical intervention or field collection, thus not requiring written consent forms. Ultimately, 137 articles were utilized in preparing this review study, and through their comparison, an extensive investigation was conducted on the epidemiology, pathogenesis, neurological symptoms, and risk factors associated with HTLV-1 infection.

Results

Virology

As a member of the genus *Retroviridae*, HTLV-1 virus (80–100 nm size) has a double-stranded positive sense RNA genome (10) that enters the host DNA and replicates dependently (11) and has envelope, matrix, capsid and nucleocapsid. The virus spreads through cell-to-cell transmission (12) as it enters adjacent cells after infecting a host cell, and thus infects multiple cells. Similar to other retroviruses such as human immunodeficiency virus (HIV), murine leukemia virus (MLV), and avian sarcomaleukosis virus (ASLV) (13), HTLV-1 predominantly infects CD4+ T lymphocytes and develops persistent infections (14). The virus has multiple genotypes, the most common of which is genotype A (15).

[DOI: 10.18502/jabs.v14i2.15749]

Pathogenesis

In summary, the virus infects astrocytes, which are the interface between the blood vessels and the central nervous system (CNS) neurons. This infection leads to excessive production of the Tax1 viral protein (a critical viral protein involved in virus attachment to host cells) within these cells. Ultimately, an over-secretion of proinflammatory mediators (16,17) occurs, resulting in the manifestation of symptoms in the CNS (18, 19). Based on research findings, the HTLV-1 Tax1 protein, which can be transmitted from cell to cell (20), induces the production of tumor necrosis factor (TNF)-α and reduces glutamate transporters (GLAST and GLT-1) in the CNS glial cells. This leads to decreased glutamate and glucose uptake, increased lactate accumulation in astrocytes, and widespread metabolic disturbances in these cells (21). Further investigations have revealed that HTLV-1-infect T lymphocytes when exposed to glial cells in a laboratory setting, trigger the release of interleukin (IL)-2 and its specific receptor, which promotes proliferation in lymphocytic cells. Addition-ally, it has been observed that IL-15 can induce a similar effect and cause self-proliferation of these infected cells (22). Patients with HAM/TSP exhibit higher levels of spontaneous proliferation in lymphocytes compared to asymptomatic individuals due to elevated levels of interferon (IFN)-γ. This higher level is attributed to the increased production of cytokines by CD8+ T cells in these patients (23). The disease is characterized by a severe and chronic inflammatory response in the CNS, resulting from the interaction between CD8+ T cells and virus-infected cells (24). Cytokines such as IL-8, CXCL9, CXCL10, and CXCL5, being higher in individuals with HAM/TSP, can recruit T cells into the CNS (25). Noticeably, more than half of the infected individuals have a mutation in the 14bp region of the HLA-G gene, which impairs the function of this molecule resulting in an increased viral load in the peripheral blood and a higher susceptibility to the viral infection (26). Further investigations have shown elevated levels of IL-2 in carriers and IFN-γ in individuals with HAM/TSP (27), while cytokines such as IL-4, IL-10, TNF-α, and IL-12 p70 exhibited non-significant changes (28). The Tax viral protein has subgroups A and B (29), which may impact the likelihood of developing HAM/TSP (30). Flow cytometry analysis comparing individuals with HAM/TSP to carriers has demonstrated higher levels of inflammatory cytokines such as IFN-γ and TNF-α in individuals with the disease (31).

Diagnosis of the virus in individuals

To diagnose the disease, a novel method called Droplet Digital PCR (ddPCR) can be utilized. In this approach, the sample obtained from peripheral blood or cerebrospinal fluid (CSF) is divided into hundreds of thousands of droplets, and then the number of viruses is determined using PCR and specific algorithms. This method can be used for patients with HAM/TSP, asymptomatic carriers, or for monitoring viral load in treated patients (32). The combination of diagnostic methods such as Western Blot (WB), PCR (tax or pol), and real-time PCR (pol) can lead to the detection of a greater number of carriers. WB was found to be effective in identifying a larger number of infected individuals, while real-time PCR can identify HTLV-1 various types (33). In a study by Nicholas Kwaan et al., it was observed that alcoholics experience long-term increases in HTLV-1 viral load, whereas this effect is reduced in individuals of African descent. This effect on HTLV-2 load is positive in smokers. Furthermore, as the viral load in peripheral blood increases, individuals become more susceptible to kidney infections (34). Considering that the viral load in peripheral blood is an indicator of disease progression (35), the TaqMan PCR technique can be employed to identify the number of tax protein molecules in the virus using highly precise measurement techniques, with a sensitivity of approximately 98% and specificity of 100%, aiding in patient evaluation (36). Based on the conducted studies, CXCL10, derived from Th1 cells and

[DOI: 10.18502/jabs.v14i2.15749]

present at high levels in the CSF of HAM/TSP patients, can be utilized as a marker for disease identification (37). Research has shown that the level of OX40 (a member of the TNF family) in the CSF of HAM/TSP patients is elevated. This response is associated with the interaction between OX40 and the tax protein of the virus in infected cells (38). Investigations have demonstrated that the viral load in peripheral blood and CSF of HAM/TSP patients is higher during symptom exacerbation, indicating increased viral load leading to symptoms exacerbation (39). Studies in Italy have revealed that SYBR Green qPCR Protocol used to measure the viral DNA in the peripheral blood of the examined individuals can serve as an alternative to the enzyme-linked immunosorbent assay (ELISA) or Western Blotting methods (40).

Epidemiology

Over the past 20,000 years, HTLV-1 has circulated among humans (41). This virus was firstly isolated from patients with cutaneous lymphoma in 1979. This virus has affected approximately 20 million individuals worldwide (42–44). Endemic regions of this disease include sub-Saharan Africa, South America, the Caribbean region, southern parts of Japan, and specific areas in the northeastern Middle East, such as Iran(45–47). The prevalence rate in endemic areas ranges from 1% to 6%, reaching 25-40% in individuals over 50 years of age. In 90% of cases, patients asymptomatic throughout their lifetime. However, symptomatic individuals may present with Adult HAM/TSP (48), uveitis (49, 50), and dermatological manifestations (51). Other disease manifestations may include myositis, rheumatoid arthritis (RA), pulmonary disease (52), Hashimoto's thyroiditis, Graves' disease, and Sjögren's syndrome (53).

Transmission Routes

The virus can be transmitted through physiological fluids such as saliva (54), blood products, and sexual contact (55). Despite the unequal prevalence in contaminated areas, environmental factors and the host genetic factors can influence the rate of viral transmission (56). A retrospective study conducted in England from 1993 to 2007 revealed that 80% of HAM/TSP patients were women, and approximately 80% of cases were attributed to breastfeeding and unprotected sexual contact (53).

Risk Factors

Considering the mode of disease transmission, the following factors can be identified as risk factors:

Immune Deficiency

Studies conducted on hemodialysis patients with positive HTLV-1 (57) have revealed higher viral load ratios compared to HTLV-1-negative individuals (903 copies per milliliter versus 117 copies per milliliter), which may be attributed to immune system deficiencies in these individuals (58). The results of studies on individuals who tested positive for pulmonary tuberculosis indicate a prevalence rate of 5.8% for HTLV-1 in these patients (59, 60). This rate is higher in older individuals and those with a family history of tuberculosis-related deaths (20, 61). Furthermore, in individuals diagnosed with sarcoidosis and tested for HTLV-1 positivity, it was found that up to 4% of all sarcoidosis patients were HTLV-1 positive (21, 62). Studies have shown that two chromosomal regions, 6q27 and 2p25, due to their involvement in the production of CCR6 (chemokine receptor 6) and ID2 (inhibitor of DNA binding 2), which are functionally impaired in individuals infected with HTLV-1, increase the likelihood of infection (63).

Contact with Blood Products

It has been unraveled that HTLV-1 positive patients have a close association with hepatitis B and C data. Accordingly, there is a strong association between HTLV-1-positive hemodialysis patients and age (64), marital status, and a history of blood transfusion (65). There was no statistically significant difference in the prevalence of HTLV-1 infection

[DOI: 10.18502/jabs.v14i2.15749]

between the northern areas of Iran and the rest of the country, where 1.4% of thalassemia major patients tested positive for the virus. However, further investigations are necessary to control blood products for these patients (66, 67).

Sexual Transmission

In investigating the rate of virus transmission through sexual intercourse, it was determined that the prevalence of HTLV-1 infection among individuals who are injection drug users is 2.1%, among men with sex with men is 1.4%, and among non-injecting drug-using heterosexuals is 0.09%. These findings indicate the role of sexual behaviors in the spread of HTLV-1 (68–70). Further studies have revealed the occurrence of HTLV-1 infection among different groups of patients, including 19.1% among injection drug users, 0.4% among men who have sex with men, 2% among female sex workers, 2.1% among individuals with tuberculosis, and 1% among individuals with sexually transmitted infections. Additionally, it has been found that hepatitis B and C viruses have the highest rates of co-infection (71, 72). The occurrence of connective tissue diseases and RA can increase the likelihood of developing HAM/TSP (73), possibly due to a higher viral load in synovial fluid as compared to peripheral blood in these individuals (74).

Global and Regional Prevalence

Among 253,855 individuals who donated blood in southeastern China, 43 individuals were found to be HTLV-1 positive, with a higher prevalence observed in the Fujian province compared to other provinces (24). Furthermore, the prevalence of HTLV-1 infection among blood donors in the provinces of Fujian and Guangdong was 2.9 and 9.9 per 10,000 individuals, respectively, which represented the highest rates among all provinces in the country. The predominant viral subtype in these areas has been identified as type A (cosmopolitan subtype) (24). In regional studies conducted in the Middle East, no cases of HTLV-1 positivity were found among individuals who donated blood in Saudi Arabia (75). Similarly, investigations in Israel focusing on blood donors revealed a prevalence of 5.8 per 100,000 individuals in the overall population. However, this prevalence varied among different ethnic populations immigrating to Israel (e.g., 50.4 among Iranian immigrants, 16 among Turkish immigrants, 10.2 among Iraqi immigrants, and 20 among South American immigrants per 100,000 individuals) (76). Lebanon reported two cases of Adult T-cell leukemia/lymphoma (ATL) that were both HTLV-1 positive, representing the first such cases in the country (77). In the endemic areas of Iran, out of 1,864,489 blood donors between 2009 and 2013, 0.098% (1,840 cases) tested positive for HTLV-1 after accounting for characteristics like age, gender, and previous blood transfusion history (27). In other epidemic areas of Iran, the prevalence of infection varied. Blood donors in the Babol district of Mazandaran province in northern Iran were tested for HTLV-1 using PCR, and the results inferred one positive case (0.2%), outlining extremely low prevalence in this location (78). Another study in Mazandaran on 288 patients with thalassemia, including 151 females and 137 males with a mean age of 21.5 ± 6.5, showed an HTLV-1 contamination rate of 6.9% (20). Another study in Mashhad, northeastern Iran, examined blood donors from 2011 to 2013, including 174,662 individuals, and con-firmed 327 cases. This study also showed that individuals with higher education levels and young blood donors require further investigations (79). In the Neyshabur region of northeastern Iran, out of 8,045 individuals from the accessible population, 6.55% were HTLV-1 and HTLV-2 positive, indicating a high prevalence of infection in this area (80–82). In Sabzevar city, northeastern Iran, among 35,067 blood donors with a mean age of 38.10 +/- 11.82 years, the prevalence of HTLV-1 was 0.19%, HTLV-2 was 0.14%, and HTLV-1/2 coinfection was 0.09% per year. Factors such as age, gender, history of blood transfusion, and

[DOI: 10.18502/jabs.v14i2.15749]

education level were found to be important in determining the prevalence (83). Investigations conducted on blood donors in Mashhad from 2011 to 2012 revealed that factors such as low income, being born in a region other than Mashhad, history of blood transfusion, and non-intravenous drug use had an impact on HTLV-1 infection rates (84). Figure 1 from the study by Gessain and O. Cassar (85) shows the geographical distribution of the HTLV-1 infections worldwide.

Based on the identified immuno-histochemical findings, the manifestations of the disease in affected individuals in the CNS and peripheral nervous systems are determined by the infiltration of mononuclear cells around the blood vessels and the degeneration of myelin and axons mediated by the secreted cytokines from these cells, which leads to the destruction of T-helper/inducer cells (86, 87). These manifestations can occur in various forms in the CNS or peripheral nervous system. For example, in a study conducted at Imam Reza Hospital in Mashhad, northeastern Iran, between 1999 and 2004, four patients were examined. These four patients all reported experiencing paresthesia and subsequent muscular weakness. Subsequently, all patients developed arthralgia, and most individuals experienced hypokinesia. The polyneuropathy involved in these patients was mostly of the sensorimotor axonal type, and it was accompanied by an increase in protein in the CSF in only one case (88). In HTLV-1-positive patients without TSP/HAM involvement, the peripheral nerves complications can reflect HTLV-1 infection (89, 90).

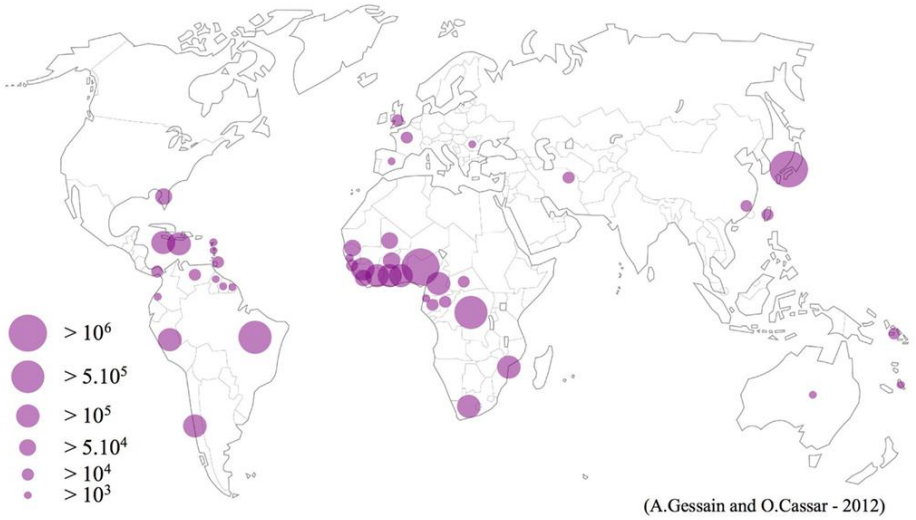

Figure 1. Geographical distribution of the HTLV-1 infection

However, in patients with HAM/TSP, it was found that 30.1% of them had peripheral involvement, which was of the sensory-motor polyneuropathy type. In the evaluation of patients with urinary problems, it was determined after urodynamic tests that a significant number of individuals examined had functional disorders characterized by excessive activity in the bladder and dysfunction of the external urinary sphincter, and these types of disorders are more commonly observed in individuals with HAM/TSP

[DOI: 10.18502/jabs.v14i2.15749]

compared to carriers (91). Considering the high prevalence of urinary symptoms in asymptomatic individuals and carriers, including dysuria, frequency, nocturia, and other related symptoms, these symptoms can be considered as the initial neurological signs in asymptomatic carriers (92). Further-more, mention can be made of cognitive impairment, which is closely associated with urinary disorders that significantly affect individuals' functional performance and quality of life (93). Various neurological manifestations and symptoms can be observed among individuals infected with HTLV-1, even without HAM/TSP (94). These symptoms include urinary symptoms, sexual disorders, lower limb weakness, and hyperreflexia in these limbs (95). Further investigations have revealed that individuals with the disease have more viral particles in their peripheral blood than asymptomatic carriers. This study demonstrated that gender and clinical symptoms similarity or age at the onset of symptoms do not impact the number of viral particles in the peripheral blood of affected individuals, but it is higher in severe motor impairment (use of wheelchair vs. walking) (96). Depression is one of the common diseases among HAM/TSP patients (about one-third), and considering the correlation between depression and poor socio-economic and psychological status of individuals and the fact that individuals with this disease are more susceptible to further disruption in socio-economic and psychological functioning, the prevalence of depression is higher in these individuals (97). One of the rare manifestations of the disease, which can occur as unilateral paralysis in the presence of progressive spasticity accompanied by hyperreflexia and is confirmed by the Electroencephalography (EEG) pattern of Guillain-Barré syndrome, can be mentioned (98). Hearing loss and tinnitus can be observed at higher rates in individuals with HAM/TSP compared to carriers or healthy individuals, possibly due to a disorder in the auditory transmission system at the cochlear or auditory nerve level (99). Neurological manifestations in HTLV-infected carriers, especially in endemic areas, may present as chronic progressive polyneuropathy (slow progressive sensory-motor dysfunction) (100). Studies have shown that most manifestations of HTLV-1 infection in affected children manifest as progressive encephalopathy, microcephaly, myelopathy, peripheral neuropathy, speech disorders, learning disabilities, and motor impairment in the form of developmental delay (101). Furthermore, studies have shown that manifestations in children can include weakness in the lower limbs, back pain, paresthesia, and hyperreflexia, which can also be accompanied by urinary disorders in children with dermatitis (102). Patients with HAM/TSP who have experienced thoracic spinal cord atrophy may exhibit neurological symptoms in the form of orthostatic hypotension resulting from dysfunction in the sympathetic-parasympathetic cardiovascular system (103). Investigations have demonstrated that an important manifestation in individuals infected with HTLV-1 is isolated peripheral neuropathy, which may serve as the sole clinical sign of the infection and should be examined in all individuals with isolated peripheral neuropathy of unknown etiology for HTLV-1 (104). Another neuro-logical sign that may indicate HTLV-1-associated neuropathic symptoms is tinnitus, which can be traced using vestibular-evoked myogenic potential (VEMP), and more than 50% of VEMP tests in individuals with HAM/TSP yield positive results (105). Visual system manifestations may present as uveitis, keratoconjunctivitis sicca, corneal changes, and interstitial keratitis. Younger individuals, those with an earlier onset age, and individuals with more severe motor impairment in HAM/TSP are more susceptible to uveitis (106). Myositis is another symptom observed in HTLV-1-infected individuals, which can result from cytokine reactions to viral products, particularly in response to the viral protein Tax. These findings confirm the pathological findings in patients, which include atrophy in muscle fibers and skeletal muscle dysfunction (107). The study findings have identified that up to 30% of patients with HAM/TSP have peripheral nerve involvement, primarily in the form of axonal neuropathy

[DOI: 10.18502/jabs.v14i2.15749]

accompanied by sensory-motor impairment (108, 109). Regarding other associated diseases, hepatitis C and infective dermatitis can be mentioned. In patients with hepatitis C who are also co-infected with HTLV-1, no significant increase in the likelihood of peripheral neuropathy or HAM/TSP involvement has been observed, but it reduces the risk of liver damage (110). Moreover, the association between infective dermatitis and HAM/TSP has been established, indicating a strong correlation between these two diseases. Therefore, investigating HTLV-1 in children with myelopathy in endemic areas is crucial (111).

Disease Diagnosis

MRI (magnetic resonance imaging) of the brain and spinal cord is a helpful diagnostic tool as it reveals evidence of spinal parenchymal atrophy in the distal segment of the spinal cord in patients with HAM/TSP (112). In individuals with urinary and sexual disorders, involvement in the central spinal region is more commonly observed, while individuals with cognitive impairments exhibit a combination of involvement in different brain regions (113). Furthermore, individuals with HAM/TSP may have multiple lesions in the brain's white matter (114). These lesions are observed in 85% of affected individuals and 80% of carriers within the white matter (115). A study conducted in Brazil in 2012 on 28 patients demonstrated involvement in the white matter (75-11%) and atrophy in these areas (14-3%), as indicated by MRI findings. It was also identified that major brain lesions exist in the periventricular regions (116). Chronic pain, presenting as either painful points or neuropathy, has been found to have the highest prevalence among individuals with HAM/TSP. This symptom can lead to increased anxiety, depression, and a decreased quality of life in affected individuals (117). Another investigation suggests that the use of MRI and a specific type of PET scan (C-PBR28 PET), employing a specific tracer leads to increased tracer uptake in the brains of patients compared to controls. Regions such as the thalamus, which has more proteins for binding to this tracer, are more prominently visualized in imaging studies (118). According to studies, the concentration of virus-infected cells in the CSF of individuals with HAM/TSP is 10% higher than that of infected cells in the blood. This percentage can aid in disease diagnosis, as individuals without symptoms have a lower percentage than 10% (119). Monitoring viral load in the peripheral blood of individuals with HAM/TSP provides no prognostic information, and instead, changes in neuro-logical and motor functions need to be assessed (96). The investigations also revealed that individuals with HAM/TSP with higher viral loads and above 50 years of age have a higher likelihood of disease progression. This increase could be attributed to increased viral DNA (deoxyribonucleic acid) production, heightened lymphocyte stimulation, and enhanced cytokine activity (120). Measurement of inflammatory cytokines such as TNF-α, β, IFN-γ, and the occurrence of the rs12979860 polymorphism (a gene associated with disease progression in IL28) in affected individuals shows a close association between TNF-α, IL6 levels, and in carriers, TNF-β, IFN-γ levels. Moreover, the occurrence of the rs12979860 poly-morphism in affected individuals was not significantly different from carriers (121).

Treatment

In a group of patients with neurogenic disorders of the bladder, characterized by dysfunction of the lower urinary system due to a neurological impairment following HTLV-1 in-fection, behavioral therapy, electrical stimulation, and exercise can lead to improvements in symptoms such as nocturia, urinary incontinence, and frequency (122). Studies have shown that a novel combination of marine algae called fucoidan (6 grams per day for 6-13 months), inhibiting the spread of HTLV-1 through cell-to-cell transmission, can reduce viral load in the peripheral blood by up to 50% in patients with HAM/TSP without affecting the immune system cells (123). In patients with lower back pain resulting from HTLV-1 infection and exhibiting motor and postural impairments, specific exercise activities, includ-

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ing Pilates exercises, can reduce the intensity of back pain and improve the quality of life for these individuals (124). Additionally, in patients with HAM/TSP, methylprednisolone pulses can be used for pain control. After receiving one gram of intravenous methylprednisolone for three days, patients demonstrated a noticeable reduction in pain and a relative improvement in walking ability (125). Considering the spontaneous proliferation of lymphocytes in HTLV-1 infection and the role of glutathione as a mediator in cellular proliferation, substances such as BSO (dl-buthionine- [S, R]-sulf-oximine) and NAC (N-acetylcysteine), which have inhibitory effects on glutathione function, can be utilized to reduce lymphocyte proliferation in the peripheral blood of carriers, thereby improving symptoms (126). The therapeutic effect of alpha interferon (three million international units for six months) in patients with HAM/TSP has demonstrated temporary effects on the motor and urinary functions of patients. Furthermore, it has been indicated to reduce viral load and levels of inflammatory cytokines such as those from CD4, CD8, CD16, and CD56 cells (127).

HTLV-1 in Iran

Based on studies examining 112 HTLV-1 sequences from Iran, it seems that the virus was most likely introduced into the country several centuries ago. This introduction may have been aided by the routes of the historical Silk Road (128). Molecular clock analyses date the time to the most recent common ancestor of Iranian HTLV-1 sequences to around 1290 AD. Phylogenetic clustering with isolates from the Middle East and Asia supports multiple early introductions, with subsequent viral spread facilitated by the Mongol invasions in the 15th century. Screening of hemodialysis patients in South Khorasan, Iran, detected a low 2.4% hepatitis C virus (HCV) infection rate, but a higher hepatitis B virus (HBV) rate of 9.75% (129). Notably, RT-PCR (Reverse transcription PCR) identified one HCV case, indicating an underestimation of HCV prevalence by serological assays in this population.

A research study conducted in Kuwait examined HTLV-1 isolates from three HAM/TSP patients, confirming the presence of the "Mashhadi" clade and indicating its regional dissemination (128). Lastly, a 36.4% HTLV antibody prevalence was found in HIV-1 infected lymphoma patients compared to 10.3% in controls, suggesting a possible association between HTLV-II and lymphomagenesis (130).

Some studies provide evidence that the prevalence of HTLV-1 infection remains considerable among high-risk populations in Iran, including blood donors, thalassemia patients, and general populations in endemic regions (131–134). Hedayati-Moghaddam et al. and Karimi et al. both noted in their studies a declining trend in HTLV-1 seroprevalence among blood donors over time, from 0.13% in 2009 down to 0.07% in 2013 (131). This trend aligns with the findings of Hezaveh et al. and Habibabadi et al., which reported low pre-valence rates of 0.09% among blood donors in northeastern Iran (133, 134). The declining prevalence could be attributed to ongoing screening of the blood supply coupled with the deferral of seropositive donors (132). However, the 2.5% prevalence detected in thalassemia patients highlights the ongoing risk of transfusion-transmitted HTLV-1 in this population (135).

Phylogenetic analysis of HTLV-1 strains in findings of the studies of Hezave et al. and Habibabadi et al. provide evidence that the virus is spreading from established endemic foci to surrounding regions (133, 134). In both studies, sequences belonged to the cosmopolitan subtype A and clustered with strains from the neighboring province of Khorasan, indicating likely expansion outward from this known endemic focus (133,134). Further genomic analysis of strains from different regions could shed light on the spread of HTLV-1 in Iran. Overall, these findings support continued screening and monitoring of high-risk groups to prevent further viral transmission.

Notably absent from these studies is longitudinal follow-up to document progression to HTLV-1-associated diseases like adult T-cell leukemia-lymphoma (ATLL) and HAM/TSP in infected individuals over time. As discussed

[DOI: 10.18502/jabs.v14i2.15749]

in the studies of Hezave et al. and Hamidi et al., the individuals analyzed were largely asymptomatic carriers (134, 135). Cohort studies monitoring development of HTLV-1 diseases could reveal important insights about viral and host factors influencing disease manifestation. Additional limitations include potential demo-graphic biases and reliance on serological screening alone without confirmatory PCR in some studies (131, 132).

A cross-sectional study by Vahidnia et al. characterized the epidemiology and neuro-logical manifestations of HTLV-1 infection in an endemic region of Iran (136). The study found high rates of HTLV-1 transmission through breastfeeding (95.9%) and infiltrative pro-cedures like dental work, hospitalization, and cupping. In 145 patients with HAM/TSP, common initial symptoms were gait impairment (72.4%), bladder dysfunction (67.8%), and sensory changes, with more severe neurologic deficits in the lower extremities. This first epidemiologic characterization of Iranian HAM/TSP patients provides crucial ground-work for future research collaborations on HTLV-1 pathogenesis and potential treatments (136).

Genetic polymorphisms may also contribute to HAM/TSP development, as demonstrated by a case-control study in Mashhad, Iran (137). Rafatpanah et al. identified associations between HAM/TSP risk and the CXCL10-1447 GG genotype as well as IL-18 -607 CC genotype. No relationships were found for other cytokine gene variants. These results suggest that certain genetic markers may identify Iranian HTLV-1 carriers at elevated risk for myelopathy. Differences compared to other populations could reflect geographic variations in HTLV-1 genetics and Iran's heterogeneous population (137). Overall, the aforementioned findings elucidate the complex interplay between viral, host, and environmental factors underlying HAM/TSP progression. Considering Iran's location and the findings of numerous studies that point to a higher prevalence of HTLV-1 infection in the country's north and northeast, it is essential to conduct more accurate screenings of people living in these parts of the country and in the overall population. In this context, implementing protocols to elevate public awareness regarding the vectors of disease transmission can be of great benefit. Additionally, due to the virus's initial involve-ment in the nervous system and the development of symptoms that predominantly cause auto-immune and sensory-motor im-pairments, all individuals who test positive for viral infection should be monitored and screened for neurological disorders, rather than repeating the reason. Novel and supportive treatments should be considered for individuals who have been diagnosed with HAM/TSP, which is the most common form of these disorders.

Conclusion

Our comprehensive review highlights the impact and risk factors associated with HTLV-1 infection in Iran and the wider Middle East region. After analyzing 137 articles spanning over two decades, we found that HTLV-1 plays a role in disorders such as HAM/TSP and peripheral neuropathy. The development of these conditions is primarily triggered by the protein Tax, which involves an interaction between viral, host, and environmental factors. Diagnostic methods primarily rely on PCR tests, imaging studies, and analysis of CSF, which have been crucial in identifying HTLV-1 infections and related neurological symptoms. While treatment approaches are still evolving, the focus is currently on managing symptoms through anti-inflammatory therapies, pain management techniques, physio-therapy sessions, and regular monitoring of disease progression. However, there is a need for targeted treatments. Main risk factors associated with HTLV-1 infection include immune deficiencies, exposure to blood products, and sexual trans-mission. This highlights the importance of raising awareness and implementing measures among high-risk populations. In Iranian regions where HTLV-1 prevalence is significant, continuous screening and monitoring strategies are essential to control the spread of this virus. Based on our review's findings, we strongly advocate for increased collaboration in research efforts, as well as public health initiatives, to gain a better understanding of and effectively combat the neurological consequences

[DOI: 10.18502/jabs.v14i2.15749]

caused by HTLV-1 infection. By gaining an understanding of the epidemiology, of how HTLV-1 develops in the body, and its clinical signs, we can improve the precision of diagnosis, create treatment options, and ultimately enhance the quality of life for individuals impacted by this virus.

Conflict of Interests

This research did not receive any specific grant from any funding agency, commercial or not-for-profit sectors. The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

We want to extend our thanks to the Library of Birjand University of Medical Sciences for their help, in granting us access to the extensive literature needed for this thorough review. We are truly grateful for their commitment, to supporting research efforts.

Author Contributions

A.R.P.S. contributed substantially to all aspects of this study, including the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the article and its revising for critical intellectual content. S.I. and L.R. made minor contributions by reviewing and editing the manuscript. H.R., as the supervisor, made substantial contributions to the conception and design of the study, revising the manuscript for important intellectual content, and gave final approval of the version to be published.

Funding

We would like to emphasize that this article was produced independently, without any financial support or sponsorship from external entities. We conducted this research and wrote this article without the influence of any financial backing or sponsorship.

Data Availability Statement

All data analyzed in this narrative review are available in the cited articles and sources. No new data was generated or analyzed as part of this review. The search strategies and criteria used to identify and select the relevant literature are described in the Methodology section.

List of Abbreviations

- DNA: Deoxyribonucleic Acid
- RNA: Ribonucleic Acid
- ASLV: Avian Sarcoma-Leukosis Virus
- HIV: Human Immunodeficiency Virus
- MLV: Murine Leukemia Viru
- $CD4^+$: Cluster of Differentiation 4 Positive
- $CD8^+$: Cluster of Differentiation 8 Positive
- GLAST: Glutamate Aspartate Transporter
- GLT1: Glutamate Transporter 1
- TNF: Tumor Necrosis Factor
- IL: Interleukin
- IFN: Interferon
- CXCL: Chemokine (C-X-C motif) Ligand
- HLA: Human Leukocyte Antigen
- WB: Western Blot
- OX40: A tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)
- SYBR: SYBR Green (a dye used in molecular biology for DNA staining)
- ELISA: Enzyme-Linked Immuno-sorbent Assay
- ATL: Adult T-cell Leukemia/ Lymphoma
- EEG: Electroencephalogram
- VEMP: Vestibular Evoked Myogenic Potential
- PET: Positron Emission Tomography
- HTLV-1: Human T-cell lymphotropic virus type 1
- HAM/TSP: HTLV-1-associated myelo-pathy/tropical spastic paraparesis
- CNS: Central nervous system
- CSF: Cerebrospinal fluid
- MRI: Magnetic resonance imaging
- PCR: Polymerase chain reaction
- ddPCR: Droplet Digital PCR

[DOI: 10.18502/jabs.v14i2.15749]

- BSO: Buthionine sulfoximine (DL-Buthionine-S R-sulfoximin)
- NAC: N-acetylcysteine

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[DOI: 10.18502/jabs.v14i2.15749]