Human T-Lymphotropic Virus, Associated Myelopathy and Leukemia: A Review

Auwal, I. Kabuga, 1 and Lawal D. Rogo2*

1 Department of Medical Microbiology and Parasitology, Faculty of Clinical Sciences, College of Health Sciences, Bayero University Kano, Nigeria 2 Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, College of Health Sciences, Bayero University Kano, Nigeria

*Correspondence Author: ldrogo.med@buk.edu.ng; lawaldahirurogo@yahoo.com
Tel. +2348039649234, +2348022569132

INTRODUCTION

The first retroviruses discovered to be associated with fatal diseases in the human population were Human- T-cell lymphotropic virus (HTLV) and immunodeficiency virus (HIV). HTLV is an envelope, positive sense, single stranded RNA (ssRNA) virus of the Oncovirinae subfamily and Retroviridae family, that reverse transcribe their RNA into DNA and integrate into the cellular DNA (Verdonck et al., 2007; Futsch et al., 2018). Five different types (HTLV-1, 2, 3, 4 and 5) have been described in humans but HTLV-1 and 2 have similar genomic structure with almost 70% homology (Fuji and Matsuoka, 2013). They are classified into a complex group of Delta retroviruses, characterized by additional non-structural regulatory tax and rex genes that play significant role in pathogenesis. They cause infection in humans by integration of proviral DNA into the somatic DNA of the host matured T-lymphocytes. Proliferation of infected lymphocytes has more important role in pathogenesis than production of free viral particles (Murphy and Bruhn, 2015). HTLV-1 and 2 have been recognized as etiologic agents of tropical spastic paraparesis, also known as Human T-lymphotropic virus associated myelopathy (HTLAM/TSP). However, HTLV 1 is implicated only in adult T cell leukemia (ATLL). HTLAM/TSP is a debilitating chronic progressive demyelinating disease that affects the spinal cord and white matter of the central nervous system; cases are mostly reported in many parts of the world. Unfortunately, even though the antiretroviral therapy have greatly improved and significantly reduced HIV progression to AIDS, such great break through is not worthy benefit for HTLV infected individuals. Thus, they are identified as severe human diseases of public health concern. This review is an overview and contains update about the biology of the virus, its interaction with the host, HAM/TSP and ATLL; their epidemiology and clinical presentations.

Key words: CD4 cells, leukaemia, lymphoma, myelopathy, oncogenic viruses, paraparesis, retroviruses, zoonosis.
The two clinical conditions are now categorized as severe human diseases of public health importance because of their associated severe immunosuppression and resistance to chemotherapy (Jamilii et al., 2015), and until now there is no known cure or protective vaccine available. In an effort to contain the situation, the Global Virus Network in 2014, launched a taskforce to promote basic research, develop new methods of prevention and treatment modalities including new public health preventive measures. Members of the taskforce were recruited from various locations across the globe as shown in figure 1 (Willems et al., 2017).

Figure 1. The global reach of the HTLV taskforce (Willems et al., 2017)

HTLV origin and basic virology

HTLV is an envelope single stranded RNA (ssRNA) virus of positive sense polarity of the Retroviridae family, Oncocirinae subfamily, genus Deltaretrovirus and Human T-cell Lymphotropic virus type specie. Seven genotypes of HTLV-1 were recognized that is HTLV-1a to g (Verdonck et al., 2007). Genotype A is the most common type. Genotypes B, D, E, F and G have merely been isolated from Central Africa while Genotype C is only present in Asia. HTLV-1 simian genotypes are interspersed in-between the human genotypes, indicating frequent zoonotic and anthroponotic transmission (Verdonck et al., 2007). Genotype A is the only known human genotype that does not have a simian relation. It is thought that genotypes B, D, E, F and G originated in Africa from intimately linked STLV about 30,000 years ago, while the Asian genotype C is considered to have originated separately in simians from Indonesia. Two subtypes, transcontinental and Japanese subgroups are found in Japan (Otani et al., 2012). HTLV-I possesses a distinctive 1.6 kb region, termed pX, which is positioned between env and the 3'LTR (Scadden et al., 2018). This area encodes a number of regulatory proteins: p40 (Tax), p27 (Rex), p21, p12, p13 and p30. The HTLV-I basic leucine zipper factor (HBZ) is encoded by the minus (complementary) strand of pX region. Of these viral proteins, Tax and HBZ are strongly implicated in pathogenesis (Scadden et al., 2018).
Figure 1. Genomic Structures of HTLV-1 (A) and HTLV-2 (B). LTR, long terminal repeat; gag, group-specific antigen whose products form the skeleton of the virion (matrix, capsid, nucleocapsid, nucleic acid-binding protein); pro, gene for protease; pol, gene for reverse transcriptase and integrase; env, envelope gene; rex, viral regulatory gene involved in promoting genomic RNA production; tax, transactivator gene; HBZ, antisense transcribed HTLV-1 basic zipper protein involved in cell proliferation; and APH-2, antisense transcribed antisense protein of HTLV-2 gene involved in transcription regulation (Murphy and Bruhn, 2018).

Pathogenesis
HTLV-1 is a provirus that passes through formation of a "virological synapse", allowing the viral genome to be passed from one cell to another. GLUT-1, a ubiquitous glucose transporter, has been recognized as a receptor for HTLV-1 (Manel et al., 2003); this may elucidate on its capability to infect different cell types. It preferentially infects CD4+ lymphocytes in vivo. It causes hematological malignancy known as adult T-cell leukemia, and an inflammatory disease in the central nervous system (CNS) called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP patients exhibit spastic paraparesis and sphincter dysfunction, as well as sensory uproar of the lower extremities, which corresponds to pathological lesions in the spinal cord. It was proposed that HTLV-1-specific inflammation induction through interaction of HTLV-1-infected CD4+ T cells and HTLV-1-specific CD8+ CTL causes bystander injury to the CNS (Kubota, 2017).

Figure 2. Life cycle of HTLV-1. Virus infection involves initial binding to cell surface of target CD4 cell, uncoating, and release of viral genetic material. Virally encoded reverse transcriptase creates a DNA copy (provirus) that is integrated into the host genome under the influence of viral integrase. Viral replication involves production of both genomic RNA and polyproteins that are cleaved by the viral protease, resulting in virion assembly at the cell surface (Murphy and Bruhn, 2018).
Epidemiology
There is no concrete data yet to represent the global prevalence of ATLL or HTLAM/TSP. Most studies carried out were centered on the epidemiology of HTLV-1 and 2. The geographical distribution of the virus has been studied for almost 35 years, since the description of HTLV-1. Estimation of global prevalence of HTLVs is based mainly on serologic screening of healthy blood donors, pregnant women and hospital patients, which might under estimate the prevalence (Mahzouneih et al., 2015). In few instances, there have been population-based studies done in villages, towns or regions in a given country with varying demographic and epidemiological characteristics.

HTLV has global distribution, with more than 20 million people carrying the infection (Willems et al., 2017); endemic areas include Central Africa, South America, the Caribbean Basin, Southern part of Iran, South Western Japan and Melanesia (Goncalves et al., 2010; Gessain and Cassar, 2012; Utsunomiya et al., 2015; Willems et al., 2017). However, only a small proportion (5-10%) of individuals carrying the virus develop clinical disease (Achiron et al., 1993; Vallinoto et al., 2015). In Asia, endemic clusters are present in Southern Japan, the Islands of Ryukyu including Okinawa, while inhabitants of People’s Republic of China and Vietnam were found free of the infection (Murphy and Bruhn, 2015). In the Americas, major endemic foci occur in the Caribbean's and cases in South America were attributed to persons of African ancestry. In Europe, occasional infections were reported among emigrants from endemic areas. In middle East, Iranian Jews from North-Eastern Iran, Mashhad, the capital city of the province of Khorasan were among those with the highest prevalence (Tabei, 2011)., Southern indies and Indonesia were reported some non-endemic foci of infection (Murphy and Bruhn, 2015). In Africa sub-region, Central Africa was tagged with the highest prevalence of 5%.

Phylogenetic studies have gone further to classify HTLV-1 into 5 major molecular and geographic sub-types. They are; (1) a cosmopolitan (C) subtype isolated all over the world (endemic to the Caribbean, South America), (2) a Japanese (J) subtype, (3) a West African (WA) subtype, (4) a Central African (CA) subtype and (5) a Melanesian (M) subtype found in Papua New Guinea, Melanesia, and Australian Aboriginals (Murphy and Bruhn, 2018). Studies of the long terminal repeat (LTR) by restriction fragment length polymorphism covering the major endemic areas demonstrated strong connection with the geographic origin of the infected individuals in comparison to the patients’ clinical status (Murphy and Bruhn, 2015). The geographic origin of HTLV-2 is less certain. It was first demonstrated in and is highly prevalent among intravenous (IV) drug users in urban North American Amerindians, Indian groups of Panama and Argentina, likewise among Bakola pygmies in Cameroon and Europe. Prevalence studies have provided basis for classifying the infection into high prevalence (more than 5%), middle (1-5%) and low (less than 1%) prevalence (Karimi et al., 2017; Santos et al., 2017; Murphy and Bruhn, 2018).

The most important routes of HTLV transmission were found to be vertical and predominantly through breast-feeding and sexual intercourse (Clark et al., 1985; Verdonck et al., 2007); uncheck blood transfusion and sharing of contaminated sharp objects such as needles and syringes are among other means (Willems et al., 2017). Intrauterine transmissions are among the newly documented routes. Sexual transmission of the virus is associated with unprotected sexual activity, multiple sexual partners, lifetime contact with infected partner and genital sores or ulcers (Goncalves et al., 2010). Other risk factors include low socioeconomic status and low literacy level. In addition, environmental factors may influence the transmission as people born in endemic areas in Iran reported a higher prevalence (Hedayat-Moghaddam et al., 2015).

Besides ATLL and HAM/TSP, infection with HTLV is associated with several other diseases of high morbidity and mortality. These include polymyositis, uveitis, infective dermatitis, crusted scabies, rheumatoid arthritis and Sjogren's syndrome (Goncalves et al., 2010), but the mechanisms leading to these conditions are currently unknown (Willems et al., 2017). Although the incidence of ATLL in HTLV-1 endemic areas is known to be high (5%) (Goncalves et al., 2010), population-based evidence concerning the incidence in non-endemic areas is scarce. In Japan, approximately 1.1 million individuals are infected with HTLV-1 and almost 1000 develop ATLL each year (Utsunomiya et al., 2015), mostly males between the ages of 24-94 years (mean age =63 years) (Fuji and Matsuoka, 2013), 20-30 years following infection, but commoner among people infected in childhood (Goncalves et al., 2010). In Iran, the average age of ATLL was 52±8 years (Akbarin et al., 2013).

HAM/TSP predominates in HTLV-1 endemic areas and in some places poor hygiene and endogamic sexual activities facilitate disease development (Safabakksh et al., 2014).
The rate at which carriers can express the neurologic disease was evaluated and approximated to 1 in 400 in elderly population of Iranian Jewish descent from Israel. This suggests that aging favors expression of the disease (Achiron et al., 1993). A prospective study at blood centers in San Francisco reveals that the incidence of HAM/TSP among healthy carriers was higher than anticipated (6 cases among 160 HTLV-1 over 10 years) (Orlandi et al., 2003). A long-term prospective study on a cohort of initially asymptomatic individuals in Brazil found that the incidence density of HAM/TSP was 5.3 cases per 1000 HTLV-1 seropositive cases per year (95% CI=2.6-10.9) (Romanelli et al., 2013). A cohort study in Brazil revealed that 75 out of 414 HTLV-1 positive patients had HAM/TSP (Tanajura et al., 2015). Among the 251 non-TSP patients followed, five developed HAM, 187 feet numbness, 130 nocturia, 127 urgency, 76 leg hyperreflexia, 53 leg weaknesses and 37 Babinski sign. Females and individuals with viral load 50,000/1,000,000 PBMC had higher risk of progression towards HAM/TSP (Tanajura et al., 2015). Among Japanese couples, only 10% of men became positive after 10 years of common life with infected woman, whereas 80% of women will develop the disease if the male partner is positive. Also, children of infected mothers, females are more often and sooner seropositive (Carles et al., 2004). Co-infection with HIV seems to increase the risk of developing HAM/TSP in HTLV-1 infected patients, younger age at presentation and a more rapid disease progression (Schutte et al., 2012). The average age of occurrence among Iranian population was 45.52±15.17 years (Akbarin et al., 2013).

**Clinical presentations**

Following infection with HTLV-1 or/and 2 most patients remain asymptomatic, only a small fraction develop disease(s), which result from the virus or host immune response. ATLL and HAM/TSP among others are now considered severe diseases, making HTLV 1 and 2 of global public health importance. In addition, HTLV causes severe subclinical immune suppression that can result in high rate of opportunistic infections such as tuberculosis and Strongyloidiasis (Gonçalves et al., 2010).

ATLL is a rare and often aggressive lymphoproliferative disease of matured T-lymphocytes that can be found in the blood (Leukemia), lymph nodes (Lymphoma), skin or and multiple areas of the body, with varying clinical features and prognosis. It is categorized into four groups based on lactate dehydrogenase, organ involvement and serum calcium, which includes acute ATLL, lymphomatous ATLL, chronic ATLL and smoldering type (Tsukasaki and Tobinai, 2014). Clinically the first two variants are classified as aggressive while the other two are indolent (Qayyum and Choi, 2014). Generally, patients with ATLL present with anaemia, peripheral lymphadenopathy, hepato-splenomegaly and skin lesions. There could be systemic manifestations involving the bone, lungs, skin, gastrointestinal tract and central nervous system. Bone involvement could be associated with hypocalcaemia as was reported in over 70% of some patients (Takatsuki et al., 1994). HAM/TSP is a slow progressive inflammatory disease that affects nerves and the spinal cord, resulting in demyelination of white and grey matter. Initial presentations include stiffness and weakness of the lower limb and lumbar pain with or without sensory presentations like tingling, burning or pinprick sensations. There may be dizziness in the early phase of the disease while urinary and sexual problems could be the presentations in some group of individuals. Autonomic dysfunction of the urinary bladder and bowel may result in frequency, urgency, urge-incontinence, post void residual urine and constipation. Urinary tract infections are common and in most cases associated with complications such as urolithiasis, vesico-ureteric reflux, hydronephrosis, pyelonephritis and chronic renal failure (Gonçalves et al., 2010).

**CONCLUSION**

Adult T-lymphotropic leukemia (ATLL) and Human T-lymphotropic virus associated myelopathy (HAM/TSP) are two severe clinical conditions associated with long-term infection with Human T-lymphotropic virus I & II which are transmitted through breast feeding, sexual intercourse and blood transfusion. ATLL is a lymphoproliferative disease in middle-aged males associated with anemia, lymphatic enlargement and hepato-splenomegaly. HAM/TSP is a neurodegenerative inflammatory disorder that is mostly seen in middle-aged women and results in upper motor neuron disease. Despite effort to achieve cure or develop a reliable vaccine, ATLL and HAM/TSP continue to be associated with severe immunosuppression and remain chemoresistant. Until now, there is no specific cure or reliable vaccine; thus, most treatments are based on immune response suppression, which do not significantly improve disease process or quality of life.

**Recommendations:**

Going by the current trend of HTLV infection and sequel, there is urgent need for public health measures to fast tract the spread of the infection and minimize complications.
Emphasis should be given on public enlightenment about modes of transmission and the health consequences, especially the long term complications. There is the need to address issues regarding reckless sexual activities, illicit use of syringes and needles, especially among intravenous drug users, unchecked blood transfusion and use of protective gadgets among health care workers and other related personnel. Furthermore, a proper global epidemiological survey, not only among blood donors but in the general population should be carried out so as to have a good picture of the problem. This will facilitate the development of reliable vaccine, antiviral agent(s) and other prevention/control measures.

REFERENCES


