Search Perspective

Human T Lymphotropic Viruses (HTLV) 1/2: A Search Perspective On Virology, Clinical Manifestations And Epidemiology in Nigeria

***Okoli RO[1], Osunde I[1], Terna GU[1]**
Department of Haematology, Faculty of Basic Clinical Sciences, Rev. Fr. Moses Orshio Adasu University, Makurdi. Nigeria

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***Correspondence:** Okoli R O
Email: okoliro@yahoo.com

ABSTRACT
Human T Lymphotropic viruses (HTLVs) are complex delta retroviridae; a family of retroviruses which includes both Simian T-Lymphotrophic Vvirus (STLV-1) and Bovine Leukaemia Vvirus (BLV). It is an enveloped virus, the only human pathogen of the subfamily Oncovirinae, which includes HTLV-1, and HTLV-2. Other new members are HTLV-3 and HTLV-4. It has a worldwide distribution affecting between 10 and 20 million people. HTLV-1 is primarily associated with adult T-cell leukaemia (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV -2 is rarely pathogenic and is sporadically associated with neurological disorders. HTLV-1 and 2 can infect T cells, B cells, monocytes, dendritic cells, synovial cells and endothelial cells and it can also cause malignant transformation in T cells. It causes a chronic lifelong infection and currently has no cure.
Keywords: Adult T-cell leukaemia, Epidemiology, Human T Lymphotropic virus-1, Human T Lymphotropic Viruse-2, HTLV-1 Associated Myelopathy, Nigeria, Tropical Spastic Paraparesis

INTRODUCTION
Human T Lymphotropic viruses (HTLVs) are complex delta retroviridae; a family of retroviruses which includes both simian T-Lymphotrophic virus (STLV-1) and bovine leukaemia virus (BLV).[1] Bovine Leukaemia Virus infection of sheep has been used as an animal model for HTLV[2]. HTLV was the first human retrovirus discovered. It is an enveloped virus, the only human pathogen of the subfamily Oncovirinae, which includes HTLV-1, and HTLV-2. Other new members are HTLV-3 and HTLV-4.[1]

In 1980, HTLV- 1 was isolated in a patient with cutaneous T-cell lymphoma and about two years later, HTLV-2 was isolated in a patient who had been diagnosed with hairy cell leukaemia.[2]

HTLV-3 and HTLV-4, were subsequently discovered in 2005 but at the moment, little is known about their epidemiology and disease-causing properties.[3] HTLV-1 is primarily associated with adult T-cell leukaemia (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV -2 is rarely pathogenic and is sporadically associated with neurological disorders. HTLV-1 and 2 can infect T cells, B cells, monocytes, dendritic cells, synovial cells and endothelial cells but it can cause malignant transformation in only T cells.[3]

VIROLOGY OF HTLV

Human T-cell leukaemia virus type 1 (HTLV-1) and type 2 (HTLV-2) have a similar genome structure and an overall nucleotide homology of approximately 70%.[4] The inner membrane of the envelope is lined by the viral matrix protein (MA) which encloses the viral capsid (CA). Within this capsid lies two identical strands of genomic RNA, protease (Pro), integrase (IN), and reverse transcriptase (RT) enzymes.[3] The retroviral genome is complex and contains genes that code for the structural proteins; gag, pro, polymerase (pol), env and non-structural proteins; regulatory proteins (tax and rex) and accessory proteins (HTLV-1; p12/27, p13/30 p13, HTLV-2; p10, p1, p11).[1,3,5]

Tax increases the rate of viral Long Terminal Repeats (LTR)-mediated transcription and modulates the transcription of numerous cellular genes involved in cell proliferation and differentiation, cell cycle control and DNA repair. Experiments suggest that Tax is essential for HTLV-1 mediated transformation of primary human T cells.[1,2,3] Unlike Tax, Rex regulates viral gene expression only post-transcriptionally by preferentially binding, stabilizing and selectively exporting intron containing viral mRNAs from the nucleus to the cytoplasm.[1,3] The roles of the accessory proteins in HTLV biology are not clearly understood. However, studies have indicated that they are important for the ability of the virus to infect, spread, and persist in vivo.[5]

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The minus strand of the pro-viral genome encodes several isoforms of the HTLV-1 basic leucine zipper factor (HBZ). HTLV-1 basic leucine zipper factor interacts with cellular factors Jun-B, c-Jun, Jun-D, cAMP response element binding (CREB) and CREB binding protein (CBP)/p300 to modulate both viral and cellular gene transcription. HBZ also plays a crucial role in T cell proliferation.[1,3] Among all the viral proteins, experimental evidence implicates Tax as the viral oncoprotein and suggests a supporting role for HBZ in the oncogenic process.[3]

EPIDEMIOLOGY OF HTLV

HTLV-1 and 2 are both involved in actively spreading epidemics, affecting 15-20 million people worldwide.[6]
However, determining the worldwide epidemiology of HTLV infections is difficult due to some of the following reasons;

Paucity of data from many regions especially the endemic regions; in some other cases, there was only a specific focus on areas of described high prevalence, distinct ancient populations, or high-risk groups through social behaviour.
Many studies were done using blood donors or pregnant women whose epidemiologic data is usually not reflective of the whole population.

The non-uniform nature of HTLV-1 distribution. It may occur as "a relatively small foci or clusters with a high or very high prevalence of infection, with nearby quite low endemic areas as exemplified in Southern Japan and in some areas of South America."

The use of diagnostic assays that lacked specificity.[7,8]
Despite the above limitations, a study making a case for HTLV-1 vaccine made an epidemiological estimate of about 10-20million HTLV-1 infections worldwide[8] while Gessain et al estimated a total of 5–10 million infections but noted that this was based on only 1.5 billion of the world's 7 billion inhabitants originating from known HTLV-1 endemic areas with reliable available epidemiological data.[7]

HTLV-1 is highly endemic in the Southwestern part of Japan, sub-Saharan Africa, South America, the Caribbean area, and foci in Middle East and Australo-Melanesia while HTLV-2 has a more restricted distribution than HTLV-1 being more prevalent among some native Americans and some Central African tribes and also being relatively commoner among intravenous drug users (IDUs) and their sex partners in Europe, North America, and other regions of the world.[9,10,11]
A few available population-based studies suggest that the prevalence of HTLV-1 infection is commoner among the older age groups, females and low socioeconomic status.[8,12,13]

MODES OF TRANSMISSION OF HTLV

These include;
Blood Transfusion: this is the highest risk factor for transmission of HTLV. It has a highly efficient mode of HTLV-1 infection with an estimated seroconversion rate of 27%–63% after exposure to HTLV-1 positive cellular blood components.[14]

In addition, HTLV related diseases develop more rapidly following blood transfusion when compared with other routes of transmission.[15]
The commonest risk factors for seroconversion following blood transfusion include; transfusion of cellular blood products (red cells, platelets, whole blood), blood stored for less than one week and immunosuppression in the recipient.[16]

Breastfeeding: risk factors for transmission of HTLV infection via breastfeeding include prolonged breastfeeding (longer than 6months of age), high pro-viral load in breastmilk and high quantities of maternal antibodies. About 10-25% of children breastfed by HTLV-1 positive mothers will be infected and intrauterine infection is less common.[7,17,18]

Sexual: Increased exposure and increased pro-viral load increase the risk of sexual transmission of HTLV. Risk of infection is higher from infected males to females than vice versa.[7,9]

Intravenous drug use: This mode of transmission is mostly linked to HTLV-2 compared to HTLV-1.[19]

Transplant: studies have documented the transmission of HTLV through transplantation of human tissues donated for transplantation.[20]

PATHOGENESIS OF HTLV.

HTLV-1 and HTLV-2 display distinct pathogenic properties in vivo but both viruses infect and transform primary human T cells in cell culture. The basis for transformation is not fully understood, but it involves the viral trans-activator protein, Tax. Several studies propose that Tax initiates the malignant process in HTLV infections by activating several points of transcriptional and post-transcriptional dysregulation in the infected T cell. It has been hypothesized that HTLV-1 is more pathogenic than HTLV-2 because of the differences in the respective Tax activities. The HTLV-1-encoded trans-activator Tax (Tax-1) and the HTLV-2 Tax (Tax-2) have ~78% homology at the amino acid level and display many properties characteristic of viral oncoproteins.[5]
Another difference between the viruses is their cell tropism. Human T-Lymphotropic Virus-1 has a preferential tropism for CD4+ T cells in both asymptomatic patients and those with neurological disease and more recent studies demonstrated that CD8+ T cells are an additional viral reservoir in vivo for HTLV-1 in HAM/TSP patients. In contrast, HTLV-2 is found primarily in CD8+ T cells in infected individuals but in some individuals, infection of CD4+ T cells has also been observed. It is noteworthy that in-vitro studies of transformation following co-culture of HTLV- producing cells with primary peripheral blood mononuclear cells have paralleled the in vivo observations.[4,5]
As earlier described, HTLV targets CD4+T cells but unlike

the retrovirus HIV-1, it has a low replication rate and hence a relatively low viral burden and high genetic stability. Secondly, HTLV-1 induces proliferation rather than death, and ultimately, transformation of infected CD4+T cells.[21]
The pathogenesis is still an area for research and attempts at describing it has been mainly in conjunction with its major associated disease entities namely ATL and HAM/TSP. A full understanding of HTLV associated diseases is impaired by the lack of suitable animal models and inaccessibility of tissue from the central nervous system of affected patients[22] but it has been proposed that the pathogenesis of these diseases is linked to very high pro-viral load and an exaggerated immune response. This holds true especially for the inflammatory disease conditions like HAM/TSP.[23]

DISEASE ASSOCIATIONS

Most carriers of HTLV remain asymptomatic for life and for those who become symptomatic, HTLV-1 is more likely to be implicated than HTLV-2 because it is more pathogenic.
The two major pathologies associated with HTLV-1 infection and present in all endemic areas are: adult T-cell leukaemia (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). Others include, uveitis, infective dermatitis, polymyositis, synovitis, thyroiditis, and bronchioalveolar pneumonitis, Sjögren syndrome, arthropathy/arthritis, strongyloides stercoralis hyperinfection, infective dermatitis e.t.c

ADULT T-CELL LEUKAEMIA/LYMPHOMA (ATL)

This develops in about 1-5% of infected persons and has an incubation period of 20-40 years. Mean age at diagnosis is between 40-60years which tends to agree with studies that suggest that ATL is more likely to develop in carriers infected in childhood than in adulthood.[21,24,25]

PATHOGENESIS

The pathogenesis of ATL involves four stages: infection, polyclonal proliferation, clinical latency and tumourigenesis.[3] HTLV transmission requires physical cell to cell contact. The structural protein, Env mediates the binding of infected cells to uninfected target cells via a GLUT -1 receptor, followed by the formation of a virological synapse, which allows the entry of viral particles, proteins and RNA into the new cells. This is followed by reverse transcription of the viral RNA into the host DNA causing an activation of the newly infected T cells via CD2/LFA-3, LFA-1/intracellular adhesion molecule (ICAM) and IL-2/IL-2R. These activated cells then form a pool of proliferating lymphoblasts that are aleukaemic and polyclonal.[3,22]
The virus proliferates and grows indefinitely (resistance to apoptosis) in the newly infected cells due to their expression of the viral genes; Tax and HBZ. This proliferation can be counterbalanced by the hosts' HTLV-1 specific immune response resulting in clinical latency. These resistant clones are prone to genetic damage and can subsequently transform into malignant cells many decades later (tumourigenesis); but this transformation occurs in only a small percentage of HTLV-1 infected individuals. The reason for this small number is largely unknown but it is known to also be mediated by Tax and HBZ.[3,22]

CLINICAL FEATURES

The clinical features include;

a. Features due to organ involvement; lymphadenopathy, hepatosplenomegaly, skin involvement (plaques, nodules, ulcers, and erythroderma), rarely, lungs, gastrointestinal tract, bones and central nervous system.
b. Hypercalcaemia; secondary to parathyroid hormone-related protein or receptor activator of nuclear factor kappa B ligand (RANKL) produced by ATL cells.
c. Immunosuppression with opportunistic infections e.g., Pneumocystis Jirovecii pneumonia, cryptococcus meningitis, disseminated herpes zoster etc.

This diversity in ATLL clinical manifestation led to its classification into four distinct subtypes viz;

1. Acute ATL
- Rapid and aggressive clinical course
- Lymphadenopathy
- Hepatosplenomegaly
- Skin lesions
- Pulmonary involvement
- Hypercalcemia with lytic bone lesions
- Has a leukaemic manifestation with <2% of ATL cells in peripheral blood associated with lymphocytosis

2. Smouldering ATL
- Indolent course
- May have skin and pulmonary involvement
- Has a leukaemic manifestation with about 5% ATL cells without lymphocytosis.
- No hypercalcemia, lymphadenopathy, or other visceral involvement
- Possible elevation of the serum lactase dehydrogenase (LDH) level

3. Chronic ATL
- Indolent course
- Possible lymphadenopathy, hepatomegaly, splenomegaly, skin or pulmonary involvement
- No hypercalcemia, ascites, or pleural effusion
- No CNS, bone, or GI involvement
- A serum lactate dehydrogenase level that may be twice the reference range
- Abnormal T-cell lymphocytes, greater than 3.5 X 109/L
- Absolute lymphocytosis, greater than 4.0×10^9/L

4. Lymphomatous ATL
- Rapid course
- Lymphadenopathy in the absence of lymphocytosis
- No leukaemic phase
- Histologic evidence of lymph node involvement required
- Skin lesions clinically indistinguishable from cutaneous T-cell lymphomas
- Hypercalcemia, raised serum LDH.

LABORATORY DIAGNOSIS OF ATL

FULL BLOOD COUNT (FBC): may be normal or show leucocytosis with absolute lymphocytosis. Cytopaenias may occur in advanced diseases.

MORPHOLOGY; shows the characteristic flower cells. These are atypical lymphocytes with abundant basophilic and agranular cytoplasm, lobulated/multiply indented nucleus with condensed chromatin and small or absent nucleolus.

IMMUNOPHENOTYPE; predominantly, the neoplastic cells are mature helper T cell hence TdT-, CD2+, CD3+, CD4+, CD5+, CD45RA+ (in blood), CD40RO+ (in LN and Skin), HLA-DR+, L-selectin+. CD 25+ in activated ATL cells, CD 52+ in most ATL cells, CCR4+ in about 90% of cases and indicates poor prognosis usually.

DETECTION of anti HTLV-1 antibodies with enzyme linked immunosorbent assays (ELISA) or particle agglutination tests. Confirmatory tests to rule false positive ELISA results include western blot, immunofluorescent assays and polymerase chain reaction (PCR).

TREATMENT OF ATL

Currently, no standard treatment regimen exists. Without treatment, most patients with acute and lymphomatous subtypes will die within weeks to months. Smouldering subtypes can survive for more than five years without treatment however, it can progress to acute and prognosis becomes very poor. Chronic ATL has the most diverse prognosis among the subtype and it can also progress to acute subtype.[24]

Modalities of treatment have been an area of intensive research and clinical trials and they include;

1. Watchful waiting; in smouldering and favourable chronic subtypes, unless disease progression sets in.
2. Chemotherapy; multi-agent chemotherapy as proposed by the Japan Clinical Oncology Group (JCOG)'s Lymphoma Study Group (LSG 15); VCAP-AMP-VECP (VCAP: vincristin, cyclophosphamide, adriamycin, prednisolone; AMP: adriamycin, ranimustine (MCNU), prednisolone; VECP: vindesin, etoposide, carboplatin, prednisolone).
3. Interferon alpha (IFN) and zidovudine (AZT) therapy
4. Allogeneic hematopoietic stem cell transplantation (allo- HSCT).

   The above modalities have all yielded varying outcomes with regards to complete remission rates however, duration of overall survival rates is still poor with some of the regimen fraught with toxic side effects. The newer modalities of treatment being investigated for its potential efficacy in managing ATL include;
5. Histone deacetylase inhibitors e.gvorinostat, panobinostat, romidepsin
6. Mononclonal antibodies (mAb) and toxic fusion proteins; LMB-2, composed of the anti-CD25murineMoAb fused to the truncated form of Pseudomonas toxin, Denileukindiftitox (DD; DAB(389)-interleukin-2 [IL-2]), an interleukin-2-diphtheria toxin fusion protein, alemtuzumab; anti-CD52 +/- CHOP, KW-0761, a next generation humanized anti-CCR4 mAb.
7. Purine analogs: pentostatin, forodesin
8. Proteasome inhibitors; bortezomib (velcade), lenalidomide (revlimid), pralatrexate (Folotyn).

HTLV-1 ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPERESIS (HAM/TSP)

This is a slowly progressive inflammatory demyelinating disease of the central nervous system.[42] About 0.25-3.8% of infected individuals develop this disease and it is commoner in females than males with an incubation period that ranges from 4months - 30 years.[26]

PATHOGENESIS

The main pathophysiological feature in HAM/TSP is that of a chronic inflammation of the white and grey matter of the spinal cord (myelo-meningitis) followed by the degeneration of the axons, usually the middle and lower thoracic vertebrae.[24,26] The exact cellular and molecular events underlying the induction of chronic inflammation in the spinal cord by HTLV- 1 are still unclear, the most widely accepted hypothesis is that HAM/TSP is the result of "bystander damage".[26]

The proposed sequence of events is as follows:

Infected CD4 T cells become activated and migrate across the blood brain barrier of the spinal cord especially the perivascular tissues and parenchyma. These cells start to express their viral antigens such as Tax and also secrete inflammatory cytokines such as IFN-Ɣ. This leads to elaboration of chemokines by the resident cells which recruit more pro-inflammatory cytokines like those of the infected CD-4 T cells and HTLV specific CD8 T cells such as IL-1B,6,12 and TNF-α. These result in an exaggerated immune inflammatory response and subsequently CNS damage (involving the neurons, astrocytes and microglia).[26]

The bystander phenomenon is used to describe the fact that the damages noted in the CNS are not due to direct destruction by the infected T cells but a secondary result of the activities of all inflammatory cytokines elaborated during the process.

CLINICAL FEATURES

Lower limb weakness (paraparesis); usually symmetrical, insidious onset, slowly progressive and usually unremitting, usually associated with gait abnormalities and falls.

Low back and lower limb pain, associated with paraesthaesia, numbness and pins and needles or burning sensation.

Features of detrusor over activity and sphincter-detrusor dyssynergy e.g urinary frequency, urgency, incontinence, retention often causing recurrent urinary tract infections.

Constipation

Erectile dysfunction

Rare features including; cerebellar signs, optic neuritis and atrophy, and nystagmus.

LABORATORY DIAGNOSIS

Full Blood Count: may be normal or show absolute or relative lymphocytosis. Anaemia may also be present.

Morphology: lymphocytes with lobulated or cleaved nucleus or flower cells similar to those in ATL may be seen in peripheral blood (PB) and cerebrospinal fluid (CSF) smear. There may also be reactive lymphocytes.

HTLV-1 antigens or antibodies may be identified from PB or CSF by ELISA. Confirmatory tests include Western blot or Immunofluorescence assays and PCR.

TREATMENT

No standard treatment regimen exists. Treatment modalities have aimed to eradicate inflammation and reduce the pro-viral burden. Several clinical trials carried out using anti-inflammatory drugs and immunomodulators e.g. corticosteroids, IFNs α and β, danazol, etc seemed to show clinical improvements but the results did not warrant recommendations as useful treatment strategies as they did not really prevent disabilities subsequently.

Some studies using combination anti-viral therapy with zidovudine and lamivudine showed no significant result in inhibiting disease progress and improving clinical outcome. The humanized anti- CCR4 monoclonal antibody is also undergoing clinical trials since the CC chemokine receptor seen in ATL patients has also been discovered in HAM/TSP patients.

THE EPIDEMIOLOGY IN ENDEMIC REGIONS AND NIGERIA

The seroprevalence of HTLV has been widely studied among blood donors and most positive results are predominantly due to HLTV-1 infection as would be seen in this review.

Seroprevalence rates among blood donors in non-endemic regions like the United States are quite low. Among 2,047,740 first-time donors, 104 were seropositive for HTLV-1 (prevalence, 5.1 cases/100 000), and 300 were seropositive for HTLV-2 (prevalence, 14.7 cases/100 000). HTLV-1 seropositivity was associated with female sex, older age, and black and Asian race/ethnicity. HTLV-2 seropositivity was associated with female sex, older age, nonwhite race/ethnicity, lower educational level, and residence in the western and southwestern United States.[14]

In endemic countries, the prevalence varies significantly even within the same country. Japan has the world's highest prevalence of HTLV-1 infection and associated diseases; notably in the southern parts where more than 10% of the general population is infected.[24] A study conducted in 2006 among blood donors showed a prevalence rate of 1.08million.[7] Rates among blood donors are about 0.12-1.29% among the males and 0.11-1.66% among the females with higher rates noted in the older age group (>60years),[16]; this age and sex distribution is similar with that seen in a US study.

In Iran, a total of 1,864,489 blood donations were obtained and evaluated from seven blood transfusion centres, for a five-year retrospective study (2009-2013). The overall HTLV-1 prevalence was 98.7 per 100,000 donations during the 5-year period. Similar to the US and Japan studies, seroprevalence was higher among females and older age group. Seroprevalence rates were also higher among married donors and first-time donors.[12]

The higher prevalence noted among the older individuals was assumed to be because of a higher number of contacts they may have had through their lifetime, while the high prevalence in females was assumed to be because of a higher tendency of viral transmission from males to females during sexual intercourse than vice versa. First time donors had higher prevalence because they lacked proper donor education that regular donors had and hence would have had more risky lifestyle behaviours. The finding among married donors was attributed to their older age and probably more sexual contacts in the past, however these findings are all subject to further investigation.[12]

Even though listed as an endemic region, Africa's paucity of data makes it difficult to ascertain prevalence rates. This is further compounded by high rates of false positive results due to malaria antigen cross reactivity.[16] However, studies suggest a wide seroprevalence in Africa ranging from low to high prevalence. For example, Okoye et al quoted low prevalence rates from studies that had been carried out in South Africa of 0%, Zimbabwe 0.11%, Mozambique 0.7% and Congo 0.7%[13] while Ma'an et al quoted high seroprevalence rates of >5% in countries like Benin, Cameroon, and Guinea Bissau.[27]

A study conducted in Cotonou, Benin Republic showed zero positivity among 1300 blood donors but a prevalence of 0.3% and 5.4% was observed in coastal and Northern provinces respectively indicating that seroprevalence rates may differ even within the same country.[27]

In Dakar, Senegal, where there have been reports of ATL, HAM and infective dermatitis, 4900 blood donors were surveyed from which only 8 donors were seropositive (HTLV-1=7 donors, HTLV-2=1 donor).[28]

In Nigeria, it varies from 0.7 to 3.7% according to geographical location.[7] In Northern Nigeria, studies from Jos showed a prevalence rate of 0% among 500 blood donors[27] while Gombe had a prevalence rate of 6.5% using Enzyme Linked Immunosorbent Assay (ELISA) and 0% on confirmation with Western Blot (WB).[15] Similarly, in Enugu, a prevalence rate of 0% was noted among 300 donors.[13] Studies from Lagos noted a rate of 1% (ELISA) and 0.5% (WB) among 210 donors[29] and 1.9% among 372 donors in Osogbo.[30]

The highest prevalence rate recorded was 25.8% (ELISA) among the 300 donors in Ogbomosho, Oyo state. Like the Iran studies, higher prevalence was noted among married donors; however, prevalence rate was higher among males because of a dearth of female donors. Higher prevalence was noted among younger donors (18-24years) because of the age discrimination during donor selection.[31]

Data on the seroprevalence of HTLV infection in SCA patients are very few. A study done by Oswaldo et al showed a prevalence rate of about 7% in 116 multiply transfused sickle cell anaemia patients while a retrospective study done in Bahia, Brazil to determine the prevalence of infection among 1415 SCA patients showed that 67 patients (4.7%) had human T-lymphotropic virus type I (HTLV-I). Also, in Martinique (French West Indies), a human T-cell leukaemia/lymphoma virus type I (HTLV-I) endemic area, it was found that 17 (10%) of 173 SCA patients had antibodies to HTLV-I. [32,33,34]

Seroprevalence rates of HTLV among patients with lymphoid malignancies showed varied results due to factors such as the country of study and sample size. In Rio de Janeiro, Brazil, the prevalence of HTLV-1 infection in 510 haematologic patients was 9.01% in which the most prevalent subgroup was T-cell disease with the prevalence of 28.9%. The reported seroprevalence of HTLV-1 in 88 patients with haematologic malignancies in south Chile

was 3.4%. A prevalence of 23% was found among 100 patients with malignant nodal lymphoma in Okinawa, Japan. Different results have also been published from different regions in Iran. For example, the prevalence of HTLV-1 infection in 101 patients with haematologic disorders, including lymphoma, leukaemia, thalassemia and haemophilia, in Isfahan was 0.99%, 20% in 60 patients with haematologic malignancies (leukaemia and lymphoma) in Tehran and 18.8% in 54 patients with non-Hodgkin lymphoma in Mashhad. [35,36,37]

A seroprevalence study of HTLV-1 and HIV infection in blood donors and patients with lymphoid malignancies in Lagos, Nigeria reported 0% in patients with lymphoid malignancies whereas a later study conducted among patients with lymphoid malignancies in Lagos reported the seroprevalence rate of HTLV-1 infection among 39 cases of lymphoid malignancies to be 5.12%.[38]

CD4 cells are important for inducing and maintaining efficient humoral and cellular immune responses to pathogens and like other human retroviruses, HTLV causes a lifelong infection of CD4 T-lymphocytes. However, unlike HIV, the immunological hallmark of HTLV infected individuals is a sustained proliferation of T-cells driven by the HTLV-1-encoded Tax protein. The subsequent transactivation of cellular genes by the Tax-encoded region can result in malignant transformation, although this is rare. In the majority of cases, cytotoxic T-cells effectively control the virus by lysis of infected lymphocytes, which in turn results in the release of inflammatory cytokines. This results in the diverse range of pathologies, including malignant disease, inflammatory syndromes, and infective complications seen in HTLV infection.[39,40]

This proliferation of CD4 cells following HTLV infections can suggest that CD4 cell counts are high in HTLV infections but there are very few documented studies on the effect of HTLV infection on CD4 count.

Goon et al tried to present direct estimates of HTLV-1 Env- and Tax-specific CD4 T-cell frequencies in patients infected with HTLV-1 and they demonstrated significantly higher frequencies of HTLV-1–specific Th1-type CD4 T cells in HAM/TSP patients than in asymptomatic HTLV-1 carriers.[40]

Other available studies were from those with HIV/HTLV co-infection and this is because both infections target the CD4 lymphocytes even though their effects are different: death and proliferation, respectively. Moreso, CD4 cell count is the most used selection criterion to deter- mine ART eligibility for HIV-infected individuals especially in resource poor environments like Africa.[39]

A study "Molecular Detection and Clinical Implications of HTLV-1 Infections among Antiretroviral Therapy-Naïve HIV-1-Infected Individuals in Abuja, Nigeria" found that the CD4 cell count in those with HTLV-1 and HIV-1 co-infection was significantly higher than those with HIV-1 mono-infection (742 vs. 340) although the CD4 count for the co-infected individuals remained within normal limits.[39] A South African study by Rego et al also had similar findings.[41]

CONCLUSION

HTLV causes a lifelong infection of T-lymphocytes and the immunological hallmark of HTLV infected individuals is a sustained proliferation of T-cells driven by the HTLV-1-encoded Tax protein. The activation of cellular genes by the Tax-encoded region results in malignant transformation, although this is rare. In the majority of cases, cytotoxic T-cells effectively control the virus by lysis of infected lymphocytes, which in turn results in the release of inflammatory cytokines. This results in the diverse range of pathologies, including malignant disease, inflammatory syndromes, and infective complications seen in HTLV infection.

RECOMMENDATIONS

Given the clinical significance of Human T-lymphotropic virus (HTLV) infection, particularly in endemic regions, the following are the proposed recommendations:

1. Enhance Surveillance and Epidemiological Studies:

There is a need for large-scale, population-based studies to accurately determine the burden of HTLV infection in Nigeria. Current data are largely derived from selected populations such as blood donors and may not reflect the true prevalence. Establishing a national HTLV surveillance system will improve data availability and guide evidence-based policy formulation.

2. If data from large-scale, population-based surveillance studies (as recommended above) demonstrate that Nigeria constitutes an endemic region, it will provide a strong basis for the following:

a. Strengthening Blood Transfusion Safety: vis a vis incorporation of mandatory routine HTLV screening into the national blood transfusion protocols. This will reduce the risk of transfusion-transmitted HTLV infection, particularly given the high efficiency of transmission through cellular blood components.

b. Maternal and Child Health Interventions: routine screening of pregnant women with appropriate counselling on the risks of mother-to-child transmission. Moreso, public health strategies will include guidance on breastfeeding practices among HTLV-positive mothers to help reduce vertical transmission.

c. Public Health Education and Risk Reduction: public awareness campaigns will be developed to educate communities on the modes of transmission of HTLV, including sexual transmission and intravenous drug use because promotion of safe sexual practices and harm-reduction strategies will be important in limiting the spread of infection.

3. Improvement in Diagnostic Capacity

Standardization and wider availability of diagnostic tools, including enzyme-linked immunosorbent assay (ELISA) and confirmatory tests such as Western blot and polymerase chain reaction (PCR), should be prioritized. This will reduce false-positive rates and improve diagnostic accuracy, particularly in malaria-endemic regions where cross-reactivity may occur.

4. Increased Clinical Awareness and Training: clinicians should be educated on the clinical spectrum of HTLV-associated diseases and consider including it in the differential diagnosis of patients presenting with unexplained myelopathy, T-cell malignancies, and recurrent or atypical infections.

5. Research into Pathogenesis and Therapeutics: further research is required to better understand the

molecular mechanisms underlying HTLV-associated diseases, including the role of pro-viral load and host immune responses. Additionally, there is a need for clinical trials to evaluate novel therapeutic approaches, as current treatment options remain limited and largely unsatisfactory.

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