Heterogeneous geographic distribution of human T-cell lymphotropic virus I (HTLV-I) and epidemiological, genomical, pathophysiologic, therapeutic knowledge about HTLV

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Abstract

Human T-Cell leukemia Virus-1 also called the adult T-cell lymphoma virus type 1, is a retrovirus of the human T-lymphotropic virus (HTLV) family, responsible for various life threatening diseases such as Adult T-cell Leukemia (ATL) chronic inflammatory CNS disease named as Tropical Spastic Parapariesis/HTLV-1 Associated Myelopathy (TSP/HAM). About 1–5% of infected persons are thought to develop cancer as a result of the infection with HTLV-I over their lifetimes. It is also observed that majority of the carriers of HTLV-1 remains asymptomatic throughout their whole life. Genetically factors and immunological status of the host determines the causation of associated diseases of HTLV-1. The objective of this review is to provide a good update on epidemiological, genomical, pathophysiologic, therapeutic knowledge about HTLV, and also provide knowledge about diagnostic suspicion and criteria, treatment, transmission and prevention of the disease.

Keywords: Leukemia, retrovirus, HTLV-1, T-cell lymphoma

Introduction

Around 1977, adult T-cell leukemia (ATL) has been reported as clinical entity, and in 1980 it is identified as human T-cell leukemia virus type 1 (HTLV-I) [1]. From last 2 decades the infection and associated diseases caused by HTLV-I thus studied extensively and a lot of the aspects then been cleared through vast researches and study programmed. However, the process by which it causes the leukemia (leukemogenesis) is still unknown [1]. The complication in ALT patients has been observed prominently reported are immunodeficiency and resistance against chemotherapy. The prognosis of this disease is also low because of these disease complications.

HTLV-1 human T-cell leukemia virus-1 is first discovered retrovirus that causes the two distinct types of human diseases [2]. The cases HTLV-1 associated disease are present in minority worldwide. Two reported diseases caused by the HTLV-1 are, a malignancy named as Adult T-cell Leukemia (ATL) chronic inflammatory CNS disease named as Tropical Spastic Parapariesis/HTLV-1 Associated Myelopathy (TSP/HAM) [3, 4]. Around 20 million people have been reported to be infected with HTLV-1 related diseases worldwide [5]. Then HTLV-I screening was proposed, developed and widely implemented in developed countries and few developing countries which are registered at high risked areas in 1986. It is also observed that majority of the carriers of HTLV-1 remains asymptomatic throughout their whole life [6].

Genetically factors and immunological status of the host determines the causation of associated diseases of HTLV-1. The knowledge about the clinical and diagnostic introduction of the HTLV virus has now become very important in many different medical disciplines. The geographical distribution of the HTLV-1 shows its prevalence rates in few countries where this disease is endemic and constantly reporting the new cases [7]. The objective of this review is to provide a good update on epidemiological, genomical, pathophysiologic, therapeutic knowledge about HTLV that may encourage the etiologic
suspicion and introduction of HTLV-1 in all its diverse and different clinical manifestation, which was not associated with HTLV in the past. This review also provides knowledge diagnostic suspicion and criteria, treatment, transmission and prevention of the disease.

History
In 1977, Takatsuki observed and manifests the distinct clinical entity in the blood of a patient and reported it. The disease caused by this distinct entity has complicated, aggressive clinical course that may confused with some other diseases. It is found infiltrate into skin, lungs, gastrointestinal tract and liver. The patient serum contained the leukemic multilobed flower like cells, along that hypercalcemia was also observed [8].

In 1980, Poiesz a patient suffering from cutaneous T-cell lymphoma contain HTLV in his T-cell lines. HTLV-1 thus became a prime interest in new researches and studies [9]. In 1981, Hinuma observed and identified the link between ALT and HTLV-I and he reported that an antibody is present against HTLV-I in effected patient serum [10]. In 1982, adult T-cell leukemia virus (ATLV) was identified by Yoshida independently. Soon, the study on the genomics and proteomics of HTLV and ATLV declared them as identical, then proposed name was HTLV type 1 [11, 12]. In 1983, whole sequence was identified by seiki and presence of unique region been revelaed, designated as pX. Many accessory genes been encoded by pX region, that Controls the viral replication and the involve in the proliferation of infected cells [13, 14]. In 1985, Gessain demonstrated that people suffering with TSP and liver. The patient serum contained the leukemic multilobed flower like cells, along that hypercalcemia was also observed [8].

Etiology
The human T-lymphotropic virus or human T-cell lymphotropic virus (HTLV) is a family of human retroviruses that is involved in the causation of a myelopathy called adult T-cell Lymphoma/leukemia and another demyelinating disease which is called as TSP/HAM: Tropical Spastic Paraparesis/ HTLV-I associated myelopathy. The HTLVs are related to the larger old group of primitive T-lymphotropic viruses (PTLVs) [8]. The first discovered human retrovirus discovered that is involved in cancer causation is HTLV-1. It belongs to the Retroviridae family, and the genus Deltaretrovirus. It is one of the retroviruses that are RNA viruses that use a special viral origin enzyme reverse transcriptase to convert their RNA strand into DNA. Then DNA subsequently incorporates into the host’s genome [12].

Epidemiology
The exact figures of people infected by HTLV worldwide are exactly unknown. It is estimated roughly estimation of infected HTLV-1 individuals are around 15 to 20 million, and distribution is heterogeneous in different areas and countries. It is observed that the many infected individuals act as the carriers of disease and remains asymptomatic throughout their lives. The estimated percentage of such carriers is given as 90% [12]. From last 3 decades the studies have been conducted on the geographical distribution of the Virus. The areas reported of highest prevalence are Japan, Africa, Caribbean islands, and South and Central America. The prevalence rates of HTLV-1 have been distributed into greater than 5% as high, 5% to 1% as low, and less than 1% as lowest [18]. The general prevalence in the population of southwestern isle of Okinawa and Shikoku is nearly 37% [11]. High cases of HTLV-1 have been tested for few Caribbean islands in research studies of general population’s blood donors or blood analyzing. In Jamaica, around 5% of prevalence is reported [16]. In Africa, the prevalence increases from the areas in north to the areas in south, varying from 0.6%. In Morocco the cases observed greater than 5%, in many sub-Saharan African countries, for example, Cameroon, Benin and Guinea-Bissau the prevalence is also high [20].

In Europe and North America, the prevalence is relatively low and limited to some groups. As in blood donors very low cases were found in France around 0.0039% and in United States around 0.025% [21, 22]. In South America, the virus was present in every country, but further studies of the general population is required to estimate the real prevalence of HTLV-1. Middle ranged prevalence was observed in blood donors from Chile i.e.
Since 1986 HTLV-1 screening knowledge has been introduced and was slowly applied worldwide. In 1993, HTLV-1 screening of blood donors was being performed regularly and strictly in all developed countries and in several developing countries where HTLV-1 is reported as endemic. Moreover, hemovigilance studies were performed, where individuals who received blood from HTLV-1 sero-positive donors, transfused before screening the blood was performed or from those repeated donors who had shown the sero conversion to HTLV, were tracked down and tested for the virus. It is observed that the population of blood donors does not play role in the estimation of prevalence in the general population. In the light of statistical figures, Brazil reported to have the largest number of seropositive individuals of HTLV-1 in the world. In non-endemic areas, certain groups should be considered as at risk, such as immigrants from endemic areas, the stranger or effected sexual partners and descendent of individuals known to be infected, sex professionals and intra venous drug users.

**Structure and Genomics of Virion**

Virion of HTLV-1 is enveloped, spherical to pleomorphic in shape, about 80-100 nm in diameter. Genome is monopartite, dimeric, linear, positive-sense ssRNA genome of size 8.5 kb, containing a 5’-cap and a 3’poly-A tail. It contains two long terminal repeats (LTRs) of about 600 n long at both ends. The LTRs consists the U3, R, and U5 regions. HTLV-1 has six identified subtypes A to F. Various studies have been performed on HTLV-1 sub typing but play a small role in the epidemiological status of the virus. The majority of infections are caused by the cosmopolitan subtype A, and there is no reported influence of others subtypes on the pathogenetic potential of HTLV-1.

The HTLV-1 provirus has a same structure to that of other retroviruses i.e. a long terminal Repeat (LTR) at both ends with internal sequences such as the gag, pol and env genes. A characteristic feature of HTLV-1 is the presence of the pX region, which is present between env and the 3’-LTR. This region encodes many accessory genes, which are tax, rex, p21, p12, p13, p30 and HBZ genes.

Among these genes, the role of tax gene is central in viral gene transcription, viral replication and the proliferation of HTLV-1-infected cells. Tax usually enhances viral gene transcription from the 5’-LTR through its interaction with cellular factors and helps in activation of different transcriptional pathways. Tax has also been observed in the inhibition of TGF-β signaling. TGF-β signaling inhibition enables HTLV-1-infected cells to escape TGF-β-mediated growth inhibition.

**Pathogenesis**

HTLV-1 usually infects variety of cells, such as T-lymphocytes, B-lymphocytes, monocytes and fibroblasts. Glucose transporter 1 (GLUT-1) has been registered as a receptor for HTLV-I and this receptor is uniformly expressed on cell surfaces. This is because of Tax gene that mainly induces the increase of CD4-positive T-lymphocytes by enhanced proliferation and suppressed apoptosis of cells. The analyses of HTLV-1 infected cells have shown that HTLV-I-infected cells form "virological synapses" with uninfected cells. This Contact formation between an infected cell and a target cell induces the accumulation of the viral proteins Env and Gag, viral RNA and microtubules, and the viral complex transfers into the target cell. So HTLV-I spreads in a cell to cell via such virological synapses.

After HTLV-I infection, viral proteins such as Tax protein are observed in promotion of the proliferation of infected cells and also play a vital role in the inhibition of apoptosis by their pleiotropic actions. As the HTLV-I provirus randomly integrated into the host genome, the identification of integration sites helps to identify each infected clone, and in tracking every infected cell.

Most importantly, the clonal expansion in carriers is directly associated with the onset of ATL infection. Thus, these different viral strategies in replication of HTLV-I-infected cells work efficiently in most of the carriers without any adverse effects but the high percentage of infected cells usually causes an excess immune reaction, leading to the severe inflammatory diseases, HAM/TSP, infective dermatitis. Moreover, such prolonged reported proliferation of infected CD4-positive T-lymphocytes results in the onset of ATL in some carriers after a long latent period.

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**Fig 3:** Natural course of HTLV-1 infection to the onset of ATL and showing the changes adopted by a cell during latency period and during leukemic stage. [40]
The expression of Tax shows few advantages and some disadvantages on HTLV-I-infected cells. Although the tax expression promotes the proliferation of infected cells, CTLs attack the Tax-expressing cells since Tax is their major target protein. Loss of Tax expression is frequently and consistently observed in leukemic cells. Three mechanisms have been defined for inactivation of Tax expression:

1. Genetic changes of the tax gene (nonsense mutations, deletions or insertions)
2. DNA methylation of the 5'-LTR
3. Deletion of the 5'-LTR

The fresh leukemic cells isolated from ATL patients, there are about 60% of cases which do not express the tax gene transcript. Interestingly, ATL cells with lost expression of the tax gene expressed its transcripts, observing that ATL cells do not silence or interrupt its transcription when the tax gene is abortive. Loss of Tax expression gives ATL cells a huge advantage for their survival because they can escape from CTLs.

HTLV-I infection shows a long lifespan on the infected cells due to the pleiotropic characteristic of Tax, which results in the increased numbers of infected cells. Such types of infected cells are necessary for the transmission of HTLV-I. These strategies to increase the number of infected cells are thought to increase the incidence of cancer in T-cells.

Host Immune Control

The host immune system, including the cellular response, against HTLV-I shows critical control over virus replication and the proliferation of infected cells. It is studied that CTLs been activated against the virus, and the main target of CTL’s found to be Tax protein.

HTLV-I is specific to CD8-positive cells and CTLs are abundant and chronically activated there. The paradox is that the concentration of Tax specific CTLs is much higher in HAM/TSP patients than in carriers. As the provirus load is usually higher in HAM/TSP patients; this suggests that the CTLs in HAM/TSP are not able to control the number of infected cells. The individuals with a low provirus load control the number of HTLV-I-infected cells successfully due to their higher CTL activities. Thus, the major determinant of the provirus load is thought to be the CTL response to HTLV-I.

Immunodeficiency is highly observed in ALTs patients, and it results in frequent opportunistic infections by several pathogens, including Pneumocystis carinii, fungus, cytomegalovirus and Strongyloides due to compromised immune system. Although the mechanism of immunodeficiency is still unknown, few previous reports have provided important clues about it. One mechanism proposed for immunodeficiency is that HTLV-I infects CD8-positive T-lymphocytes, which may impair the function of other immune cells. Another mechanism proposed for immunodeficiency is that the concentration of naive T-cells decreases in individuals that are infected with HTLV-I through decreased thymopoiesis. In addition, CD4+ and CD25+ T-lymphocytes are known to be as immune regulatory T-cells that control the immune system. Regulatory T-cells suppress the immune reaction by the expression of immune regulatory molecules on their surfaces. Such type of ATL cells are thought to suppress the immune response through the expression of immune regulatory molecules on their surfaces, and production of immunosuppressive cytokines.

Pathophysiology

A person who shows signs or symptoms is exposed to the infection for long periods before it manifests. A variety of factors are involved in the virus/host interaction and in transition from the asymptomatic state to the emergence of a disease associated with HTLV-I. In the aggressive forms (lymphomatous and acute types), half of the patients show adynamia, lymphadenomagia, adynamia, hepatosplenomagia, bone, skin and multiple visceral lesions and hypercalcemia. In the lymphomatous form, superficial or deep lymph node chains are observed. In the chronic form, the unspecific symptoms are observed, there is no tumor mass presence, and the skin alterations are predominant, plaques, tumor, or long-time erythroderma.

In HAM/TSP the early symptoms observed are pain in lumber region and lower limbs weakness. The early complains registered usually are burning, tingling, pin and needles or sensory pains. In several patients, first symptoms appear as urinary and sexual problems. The weakness in the lower limbs is related with moderate to severe spasticity, Babinski’s sign, and hyperreflexia. Spasticity is reported as a serious problem. It usually occurs due to a velocity dependent increase in the muscle tone in response to passive movement that plays a major role in the disability.

Urinary tract infections are commonly observed and are complicated by lithiasis, chronic pyelonephritis, and chronic renal failure. Constipation is usually very common bowel dysfunction. Neuropathic pain is very common in the late stages of myelopathy. Dyesthesias is chronic and debilitating pain. It can be affected by the weather, anxiety, stress, or musculoskeletal Stimulus. In several patients, the urinary problems or the lumbar pain may be more disabling than the leg weakness.

Diagnosis

Commonly used screening tests for HTLV-1 are Particle Agglutination Assay (PA) and Enzyme Linked Immunoassay (EIA). EIA is used for testing both HTLV type 1 and HTLV type 2, whereas PA test usually used for only HTLV type 1-HTLV type 1 and 2 can be differentiated by confirmation tests. The tests used commonly for typing are Radio Immune Precipitation Assay (RIPA), Western Blotting (WB) and Immune Fluorescence Assay (IFA). Sometimes the tests come up with indeterminate results, different reasons have been interpreted for such results that include the presence of variant strains of virus, non-specific Ag-Ab reactions and a long window period or latency period. PCR also used as a confirmatory test that usually detects the genome of HTLV-1, is a highly rated confirmatory and specific test.

The detection of HTLV-1 DNA through monoclonal insertion into the tumor cells in case of tumor is highly applicable. Increase in leukocyte counts and presence of CD-25 cells and skin lesions have been observed in few patents, but not in all patients. Biopsy should also be considered for testing the suspicious skin lesions. The tissues involved frequently are the skin, spleen, liver, lungs, GIT tract, bone, bone marrow, lymph nodes and CNS.

Diagnosis of neurological diseases that is related with HTLV usually starts from an initial findings of HTLV infection, also usually confirmed by serological and molecular methods in peripheral blood, when there are one or more of the neurological syndromes present so far and also differential diagnosis with other causes of myelopathy, deficiencies
(vitamin B12 and folate), toxicity (alcoholism), vascular/metabolic causes (Diabetes mellitus, uremia and thyroid dysfunctions), autoimmunity (connective tissue diseases, paraneoplastic conditions and some others disorders), infections and parasites (syphilis, HIV) [60]. Magnetic Resonance Imaging (MRI) and neuro physiological tests development has improved the conformation of neurological disorders and make easy to interpret the neurotic pathology in TSP/HAM patients [61]. Cerebrospinal Fluid (CSF) examination shows a mild increase in some proteins, moderate lymphocytic pleocytosis, oligoclonal bands formation and presence of HTLV-1 specific antibodies. In CSF cells of TSP/HAM patients the proviruses of HTLV-1 are found. The progression in myelopathy shows a direct relation with the increase in proviral load in the fluid or serum of the patient [60].

**Treatment**

A lot of developments have been done in search of treatment for HTLV-1 patients, despite prognosis is still very poor for ALT [1]. The huge variety of therapeutic researches had been conducted over the past decades. Those Patients who have aggressive ATL shows very poor prognosis because of multi organ, hyper-calcemia, and complications of malignant cells shows the multi-drug resistance, resulting in rapid progressing HAM/TSP, possibly because of the immune suppression that transplant patients undergo [27, 71]. There are few cases of post transfusion ATL.

**Management of Infection**

There are no vaccines available for HTLV-1 yet and prognostic knowledge is still very poor for ALT and TSP/HAM. Management of this disease involves different important intervention, such as educating the high risked individuals and counseling with the population about the control prevention and consequences of disease [72]. In 1986, Japan and other countries where the disease is reported as endemic, implement few preventive measures; the paramount important implementation was screening the blood of donors for presence of HTLV-1 in their serum thus preventing the transmission through transfusion of blood [73]. Screening of blood has proven as the most effective and best strategy in preventing the transmission of HTLV-1. However, the expensive high-cost kits for screening of the blood donors in developing countries need a special look, for solving this issue these high-cost kits were been imported to those countries [74].

The cross-feeding should also be prevented until “milk mother” not screened for HTLV-1. Another option is been proposed to the pregnant infected or carrier mothers is cesarean section which is very helpful in minimizing the vertical transmission [75]. Intravenous drug users (IDU) should also be educated on the harms, risks and consequences of such practices; it is also effective in the control of HTLV-1 transmission in population. Some social and psychological problems have been observed commonly in infected persons such as depression, anxiety that can make difficult in establishing and maintaining the relationships. The common fear about the sex and pregnancy in HTLV-1 infected individuals is observed. These all problems should be dealt properly by educating the population and counseling with the infected people. Importantly, good and complete knowledge about HTLV infection should be provided. HTLV-1 is generally confused with HIV in medical faculties; the wrong clinical manifestation stressed the patient with guilt and self-destruction thoughts, and it also makes the complications in treatment of the disease [76].

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**Conclusion**

Our study concluded that severe diseases may associate with HTLV-I infection especially endemic countries are more susceptible to such associated diseases. Prevention measures should be taken in such endemic countries to eradicate HTLV and also diseases associated to this HTLV. Some of preventive measures include screening of blood donors, screening of pregnant women and safe sex practices should acquire to prevent transmission through sexual transmission.

**References**


