

## Human T-lymphotropic virus type 1-associated myelopathy/ tropical spastic paraparesis: Clinical presentation and pathophysiology

Jean-Pierre Louboutin

Jean-Pierre Louboutin, Department of Basic Medical Sciences, University of the West Indies, Mona Campus, Kingston 7, Jamaica

Author contributions: Louboutin JP wrote the paper.

Conflict-of-interest statement: There is no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Jean-Pierre Louboutin, MD, PhD, Department of Basic Medical Sciences, University of the West Indies, Mona Campus, Kingston 7, Jamaica. [jplouboutin@hotmail.com](mailto:jplouboutin@hotmail.com)  
Telephone: +1-876-3680554

Received: February 1, 2015

Peer-review started: February 2, 2015

First decision: March 6, 2015

Revised: March 30, 2015

Accepted: July 7, 2015

Article in press: July 8, 2015

Published online: September 28, 2015

### Abstract

Human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a slowly progressive neurodegenerative disorder in which lesions of the central nervous system cause progressive weakness, stiffness, and a lower limb spastic paraparesis. In some cases, polymyositis, inclusion body

myositis, or amyotrophic lateral sclerosis-like syndromes are associated with HTLV-1. TSP was first described in Jamaica in 1888 and known as Jamaican peripheral neuritis before TSP was related to HTLV-1 virus, the first retrovirus being identified, and the disease is since named HAM/TSP. There is no established treatment program for HAM/TSP. Prevention is difficult in low-income patients (*i.e.*, HTLV-1 infected breast feeding mothers in rural areas, sex workers). Thus, there is a need for new therapeutic avenues. Therapeutic approaches must be based on a better understanding, not only of clinical and clinicopathological data, but also of the pathophysiology of the affection. Consequently, a better understanding of existing or newly developed animal models of HAM/TSP is a prerequisite step in the development of new treatments.

**Key words:** Tropical spastic paraparesis; Human T-cell lymphotropic virus type-1; Polymyositis; Animal models; Retroviruses; Myelopathy; Human T-cell lymphotropic virus type 1-associated myelopathy; Pathogenesis

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Human T-cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a slowly progressive neurodegenerative disorder in which lesions of the central nervous system cause progressive weakness, stiffness, and a lower limb spastic paraparesis. There is no established treatment program for HAM/TSP. Prevention is difficult in low-income patients. Thus, there is a need for new therapeutic avenues that must be based on a better understanding, not only of clinical and clinicopathological data, but also of the pathophysiology of the affection. Consequently, a better understanding of existing or newly developed animal models of HAM/TSP is a prerequisite step in the development of new treatments.

Louboutin JP. Human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis: Clinical presentation and pathophysiology. *World J Neurol* 2015; 5(3): 68-73 Available from: URL: <http://www.wjgnet.com/2218-6212/full/v5/i3/68.htm> DOI: <http://dx.doi.org/10.5316/wjn.v5.i3.68>

## INTRODUCTION

Human T-cell lymphotropic virus type 1 or human T-lymphotropic virus type 1 (HTLV-1), (also called the adult T-cell lymphoma virus type 1) is a retrovirus belonging to the family retroviridae and to the genus deltaretrovirus. HTLV-1 was the first identified human retrovirus and is the etiological agent of two distinct diseases: Adult T-cell Leukemia/Lymphoma (ATL) and HTLV-1-Associated myelopathy/tropical spastic paraparesis (HAM/TSP)<sup>[1]</sup>. It is estimated that HTLV-1 infects approximately 10-20 millions individuals worldwide<sup>[2]</sup>. Endemic areas include Japan, Brazil, the Caribbean, inter-tropical Africa, Eastern Europe, and the Middle East. In United States, Canada and Western Europe, it appears that HTLV-1 is mainly found in immigrants. It seems however that there is a cluster of HAM/TSP cases in Romania. One to 5 percent of the individuals infected with HTLV-1 eventually develop ATL, an aggressive malignancy of mature activated CD4<sup>+</sup> T cells, characterized by frequent visceral involvement, and opportunistic infections secondary to T cell immunosuppression. One to four per cents of patients infected by HTLV-1 will develop HAM/TSP<sup>[2]</sup>. TSP was first described in Jamaica in 1888 and was known as Jamaican peripheral neuritis before TSP was related to HTLV-1 in patients from Martinique presenting similar symptoms<sup>[1]</sup>; the affection was then called HAM. Large cohorts of patients with TSP have been reported in Jamaica<sup>[3]</sup>. HAM/TSP seems more common in lower socio-economic groups and more prevalent in rural regions. Currently, there is no established treatment program for this disorder. Prevention is difficult in low-income patients (*i.e.*, HTLV-1 infected breast feeding mothers in rural areas, sex workers). Even if the incidence is currently lower due to detection of HTLV-1-positive blood donors, there are still numerous cases of HAM/TSP.

## CLINICAL PRESENTATION

Infection of HTLV-1 can be spread through contaminated blood products, passage from mother to child and sexual transmission. Very high rates of transmission of HTLV-1 are observed with blood products containing infected cells, as well as after transplantation of organs from HTLV-1 positive patients. However, blood screening prior to transfusion reduces the rate of transmission through infected blood products. Viral transmission can also occur through the use of injected drugs. Sexual transmission is mostly male to female, and explains the increasing numbers of HTLV-1 positive women,

particularly in sex workers. Passage from mother to child can occur within the womb, by perinatal transmission, or *via* breastfeeding, particularly if prolonged after 6 mo of age, and if the proviral load is high in the milk. In Jamaica, HAM/TSP seem to be more frequent in rural areas and in low income patients<sup>[3]</sup>.

HAM/TSP is a slowly progressive neurodegenerative disorder in which lesions in the central nervous system (CNS) predominate in the lower spinal cord and cause progressive weakness, difficulty walking, stiffness, and a lower limb spastic paraparesis. Foot dragging, difficulty running, impairment of ambulation, are present in 60%-80% of cases. Weakness usually begins on one side, then extends to the other side over months or years. Pyramidal signs, paraparesis and urinary symptoms are observed in almost 100% of cases. Legs are uniformly involved but arms are weak in up to 33% of patients. Hyperreflexia of lower limbs and Babinski sign are present in more than 90% of cases. Sensory signs (paresthesia and sensory cord levels) are less frequent (25%-78%). Pain and muscle atrophy are less common. Disability occurs during the first year of the disease. The disease is progressive without remissions. The WHO diagnostic criteria for HAM/TSP require presence of paraparesis (associated or not with sensory and/or autonomic abnormalities), positive serology for HTLV-1, and presence of the virus in the cerebrospinal fluid<sup>[4]</sup>.

In addition to the typical HAM/TSP, there are some neurological manifestations related to HTLV-1, but without the typical form. Manifestations of autonomic dysfunctions (overactive bladder, heart rate and blood pressure dysregulation, erectile dysfunction, constipation), and sensory dysfunction (impaired proprioceptive and vibratory function) can be observed without HAM/TSP. Overactive bladder, characterized by incontinence, nocturia, and urgency, is one of the most common symptoms in patients without paraparesis. In some cases, overactive bladder precede HAM/TSP by years, being the initial manifestation of the disease. Patients with neurological symptoms not fulfilling the typical HAM/TSP criteria can be classified as possible or probable HAM/TSP<sup>[4-6]</sup>.

Other neurological symptoms linked to HTLV-1, but not related to myelopathy have also been reported. Cognitive dysfunction (impairment of visual and verbal memory, abnormalities of attention, and Mini-Mental State Exam), as well as cerebellar ataxia (mostly vermian cerebellar syndrome, frequently progressing to HAM/TSP, suggesting a spinocerebellar syndrome) have been associated to HTLV-1. Rare amyotrophic lateral sclerosis (ALS)-like syndromes have been described, but they differ from typical ALS by a long-term survival, and the presence of overactive bladder. Polyneuropathy, mostly sensory-motor polyneuropathy, can be associated to HTLV-1. Peripheral neuropathy (predominantly axonal) can be found in 30% of patients with HAM/TSP, but more rarely in patients without HAM/TSP (6%). Cases of cranial mononeuropathy,

usually facial nerve palsy, have been reported; a study in Trinidad and Tobago found that 21% of cases of facial nerve palsy were associated with HTLV-1<sup>[4-6]</sup>. In some cases, polymyositis, and inclusion body myositis, are related to HTLV-1, but are usually not associated with HAM/TSP. In Jamaica, 85% of patients with polymyositis are HTLV-1-positive<sup>[7]</sup>.

Symptoms usually begin around age 30. Most patients have insidious course progressing over months to years. Median time from onset to use of a cane is 6 years, a walker at 13 years, and a wheelchair at 21 years<sup>[8,9]</sup>. About 10%-20% progress to severe gait impairment over 1-3 mo. More rapid progression tend to occur in patients older than 50 with a high viral load<sup>[8]</sup>, or after blood transfusion<sup>[10]</sup>, or organ transplantation<sup>[11]</sup>. However, onset and course are highly variable. Disease usually begins with asymmetric leg weakness and stiffness. Progressively, other leg becomes involved over months or years. Spasticity then becomes more pronounced and impairment of ambulation soon appears<sup>[6]</sup>.

Routine CSF analysis may be normal or show various abnormalities. Glucose level is normal. Protein is elevated in up to 40% of patients. Cell counts are elevated in up to 57% of patients, consisting entirely of mononuclear cells<sup>[12]</sup>. Elevated intrathecal production of IgG (IgG index, oligoclonal IgG, or CSF IgG synthesis rate) occurs in 20%-85% of cases. Proviral load in CSF cells is higher than peripheral blood mononuclear cells<sup>[6]</sup>. Brain MRI abnormalities are frequently seen (from 25% to 80% of patients)<sup>[13]</sup>. T2 protocols are more sensitive to demonstrate lesions appearing as T2 hyperintense signal abnormalities. Lesions, frequently multifocal, are observed in subcortical, periventricular and deep cerebral areas. White matter lesions are also frequent in HTLV-1 carriers, and the lesions in this group are similar to the ones in HAM/TSP patients<sup>[13]</sup>. Electroencephalogram (EEG), and pathologic evaluation have shown a widespread involvement of the CNS. Diffuse EEG abnormalities (poor organization or slowing of background activity to that bursts and/or spikes) have been reported in 64% of patients<sup>[14]</sup>. Evoked potentials, particularly somatosensory evoked potentials (SSEPs) are frequently abnormal<sup>[15]</sup>.

Many disorders can be discussed in patients presenting with progressive or mildly relapsing myelopathy: multiple sclerosis, Lyme disease, vitamin B12 deficiency, human immunodeficiency virus (HIV) infection, spinal cord compression. Konzo is a form of spasticity prevalent in Africa associated with excessive consumption of cassava and chronic cyanide intoxication.

Besides HTLV-1, myelopathies are rarely related to viral infections. Rare cases of tropical spastic paraparesis are caused by HTLV-2. Double infection with HTLV-1/HIV-1 is not infrequent in areas with high prevalence of acquired immune deficiency syndrome<sup>[16]</sup>. Other viral infections are uncommon causes of acute myelopathies (e.g., poliomyelitis, herpesviruses). Besides poliovirus, flaviviruses (including West Nile virus), enterovirus-71, and cocksackieviruses A and B can induced anterior

horn cell necrosis<sup>[16]</sup>.

However, residence in a high seroprevalence endemic area, history of transfusion exposure, or IV drug abuse, or working as a sex worker, is highly indicative of the disease. CSF with inflammation and intrathecal production of IgG, abnormalities of SSEPs, hyperintense T2 signals or spinal cord atrophy on MRI are suggestive as well. Other associated systemic manifestations (*i.e.*, persistent prostatitis, dermatitis, bronchoalveolitis) can lead to the diagnosis that will be confirmed by an immunoassay and Western-blot showing HTLV-1 specific antibodies<sup>[4-6,16]</sup>. The Western-blot analysis differentiates HTLV-1 from HTLV-2 infection. Study of the CSF is the mandatory step to confirm the diagnosis. Polymerase chain reaction on CSF cells will confirm the diagnosis of CNS infection and help to distinguish HTLV-1 from HTLV-2<sup>[4-6,16]</sup>.

## PATHOGENESIS

There are different theories regarding the disease hypothesis. The most widely accepted theory related to HAM/TSP is that of a virally induced, cytotoxic, demyelinating inflammatory process of a chronic and progressive nature affecting the spinal cord. The infection by HTLV-1 triggers an antigen-specific immune response towards the HTLV-1 antigen. Cytotoxic CD8<sup>+</sup> T-lymphocytes of the host's immune response release cytokines in an effort to fight the infection. These cytokines facilitate the migration of lymphocytes across the blood-brain barrier (BBB). Demyelination is brought as a result of bystander cell injury, probably by apoptosis of oligodendrocytes. Activated microglia are a prominent feature found in the spinal cord of patients with HAM/TSP<sup>[17]</sup>. However, the role of microglia is not totally clear. Cells of microglia/macrophage lineage might be one of viral reservoirs in the spinal cords in HAM rat disease<sup>[18]</sup>. However, this point is somehow still debated. Unlike most other viruses, cell-free HTLV-1 is poorly infectious and efficient infection requires cell-cell contact. In the brain of some HAM/TSP patients, astrocytes are infected with HTLV-1. However, HTLV-1 is primarily found in CD4<sup>+</sup> T cells. Although CD4<sup>+</sup> T cells are the major reservoir, other hematopoietic cells (CD8<sup>+</sup> T cells, B lymphocytes, monocytes, macrophages, dendritic cells) and microglial cells have been infected with HTLV-1<sup>[19-23]</sup>. There are conflicting reports concerning the potential of HTLV-1 to infect microglial cells<sup>[24,25]</sup>. In one patient co-infected by HIV-1 and HTLV-1, presenting with HAM/TSP and HAND, HTLV-1 was localized to astrocytes and HIV-1 to microglia/macrophages<sup>[26]</sup>. In an attempt to study Tax-induced production of cytokines in human microglial cells and astrocytes, transduction of these cells has been done by using lentiviral vectors stably expressing Tax (oncoprotein of HTLV-1) gene. Results show that Tax can up-regulate cellular proinflammatory cytokine expression profile in human microglial cells and human fetal astrocytes<sup>[27]</sup>. However, HTLV-1 specific CD8<sup>+</sup> lymphocytes that secrete the neurotoxic cytokines

interferon-gamma (IFN-gamma) and tumour necrosis factor (TNF) are present<sup>[28]</sup> and may be responsible for bystander damage<sup>[29,30]</sup>. Extracellular Tax released from infiltrating T cells could induce cytokine release by microglia and contribute to demyelination and inflammation in the absence of detectable virus<sup>[31]</sup>. Like in other neurodegenerative diseases, it is possible that, associated with neuroinflammation, oxidative stress plays a role in the pathogenesis of HAM/TSP.

If the pathogenesis of HAM/TSP is still unknown, more data are available concerning the events leading to ATL. The pathogenesis of ATL results from the malignant transformation of CD4-positive cells. Tax induces this transformation by binding to transcription factors to promote transcription of the proviral genome. However, Tax has many other effects from repressing genes involved in DNA repair and activation of apoptosis, to inhibition of proteins involved in tumor suppression<sup>[32]</sup>. The distribution of proviral integration site is different between asymptomatic carriers, HAM/TSP and ATL patients<sup>[33]</sup>.

## ANIMAL MODELS

A number of various animal models have been developed for HAM/TSP. However, none of these models fully recapitulates HTLV-1-associated disease. Injection of immortalized MT-2 cells infected with HTLV-1 has been used in numerous experiments. ICR mice have been immunized with HTLV-I carrier T lymphocytes (MT-2 cell line) and then inoculated intracerebrally with these cells. In this experiment, perivascular cell infiltration was observed diffusely throughout the brain for over 2 wk<sup>[34]</sup>. HTLV-I antigens were detected in both sides of the cerebral hemisphere and tissue damage consisting of demyelination, axonal degeneration, and astrogliosis was observed most heavily between days 10 and 14<sup>[34]</sup>. Intraperitoneal (*ip*) inoculation of immortalized MT-2 cells infected with HTLV-1 in newborn WKAH rats can induce a chronic progressive myeloneuropathy with spastic paraparesis linked to apoptosis of oligodendrocytes in anterior funiculi of upper thoracic spinal cord. However, these signs appear 15-22 mo after inoculation<sup>[35,36]</sup>. The same animal model is characterized by activation of TNF-alpha and pX (area of HTLV-1 genome where genes for Tax and Rex regulatory proteins are located) genes<sup>[37,38]</sup>. Mononuclear infiltration was seen in the animal model previously described. Activated microglial cells and macrophages were observed 15 mo after HTLV-1 injection in WKAH rats. IFN-gamma can protect against the development of HAM rat disease<sup>[39]</sup>. If all these results are important, they have been obtained mainly in WKAH rats, mostly injected *ip* few days after birth, and signs appear more than one year after inoculation of immortalized MT-2 cells infected with HTLV-1.

Intravenous (*iv*) injection of whole blood from HAM/TSP patients or cells infected with HTLV-1 gives conflicting results<sup>[40-42]</sup>. However, these findings support the human evolution of the disease with its expression

during adult or older adult age, as observed in rats aged 12 to 15 mo, corresponding on a human scale to 40 to 60 years of age. Besides presenting tumors, Tax (oncoprotein of HTLV-1) transgenic mice can develop a disease characterized by degeneration of oxidative muscle fibers or symmetrical paraparesis of the hind limbs<sup>[43]</sup>. Inoculation of HTLV-1 in monkeys induced poly-myositis<sup>[44]</sup>.

New ways of inoculating HTLV-1 should be investigated. HTLV-1-infected MT-2 cells have been used so far; however, most of the work has been done in newborn WKAH rats injected *ip* with these cells and HAM/TSP appears after at least one year in this model. The BBB might prevent HTLV-1-infected MT-2 to reach the CNS. It has been shown that faster and more reproducible results were obtained in adult mice with a direct intra-cerebral injection of these cells<sup>[18]</sup>, suggesting that BBB might be a critical factor. In fact, it has been shown that human endothelial cells can be infected *in vitro* by HTLV-1<sup>[45]</sup>, and that co-cultures of HTLV-1 and with human brain endothelial cell line leads to loss of tight junction proteins<sup>[2]</sup>. However, these results have been obtained *in vitro*. One way to circumvent the BBB would be to cause a breach of it for example by using an *ip* administration of mannitol before injecting HTLV-1-infected MT-2<sup>[46]</sup>. Inoculating cells in the cisterna magna, an area close to the spinal cord, following *ip* injection of mannitol would be less traumatic and more simple than directly into the brain or lateral ventricle<sup>[47]</sup>. Alternatively, *iv* injection of whole blood of patients with prior administration of mannitol, could be realized<sup>[48]</sup>. Moreover, it has been shown *in vitro* that BBB is abnormal in HTLV-1 related injury, and the previously described models could mimic these features<sup>[2]</sup>.

In conclusion, more studies are necessary to define the pathophysiology of HAM/TSP<sup>[49]</sup>. Better animal models can pave the way for novel therapeutic approaches.

## REFERENCES

- 1 Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, de Thé G. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* 1985; **2**: 407-410 [PMID: 2863442 DOI: 10.1016/S0140-6736(85)92734-5]
- 2 Afonso PV, Ozden S, Cumont MC, Seilhean D, Cartier L, Rezaie P, Mason S, Lambert S, Huerre M, Gessain A, Couraud PO, Pique C, Ceccaldi PE, Romero IA. Alteration of blood-brain barrier integrity by retroviral infection. *PLoS Pathog* 2008; **4**: e1000205 [PMID: 19008946 DOI: 10.1371/journal.ppat.1000205]
- 3 Smikle MF, Barton EN, Morgan OC, Luseko J, Bailey VE, Williams EM. The significance of immune disorder in tropical spastic paraparesis. *Hum Antibodies* 1999; **9**: 133-137 [PMID: 10405834]
- 4 World Health Organization. Virus diseases: Human T-lymphotropic virus type I, HTLV-I. *WHO Weekly Epidemiol Rec* 1989; **49**: 382
- 5 Souza A, Tanajura D, Toledo-Cornell C, Santos S, Carvalho EM. Immunopathogenesis and neurological manifestations associated to HTLV-1 infection. *Rev Soc Bras Med Trop* 2012; **45**: 545-552 [PMID: 23152334 DOI: 10.1590/S0037-86822012000500002]
- 6 McKendall RR. Neurologic disease due to HTLV-1 infection.

- Handb Clin Neurol* 2014; **123**: 507-530 [PMID: 25015502 DOI: 10.1016/B978-0-444-53488-0.00024-9]
- 7 **Morgan OS**, Rodgers-Johnson P, Mora C, Char G. HTLV-1 and polymyositis in Jamaica. *Lancet* 1989; **2**: 1184-1187 [PMID: 2572904 DOI: 10.1016/S0140-6736(89)91793-5]
  - 8 **Olindo S**, Cabre P, Lézin A, Merle H, Saint-Vil M, Signate A, Bonnan M, Chalon A, Magnani L, Cesaire R, Smadja D. Natural history of human T-lymphotropic virus 1-associated myelopathy: a 14-year follow-up study. *Arch Neurol* 2006; **63**: 1560-1566 [PMID: 17101824 DOI: 10.1001/archneur.63.11.1560]
  - 9 **Osame M**, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M. HTLV-I associated myelopathy, a new clinical entity. *Lancet* 1986; **1**: 1031-1032 [PMID: 2871307 DOI: 10.1016/S0140-6736(86)91298-5]
  - 10 **Osame M**, Izumo S, Igata A, Matsumoto M, Matsumoto T, Sonoda S, Tara M, Shibata Y. Blood transfusion and HTLV-I associated myelopathy. *Lancet* 1986; **2**: 104-105 [PMID: 2873363 DOI: 10.1016/S0140-6736(86)91636-3]
  - 11 **Cabre P**, Smadja D, Cabié A, Newton CR. HTLV-1 and HIV infections of the central nervous system in tropical areas. *J Neurol Neurosurg Psychiatry* 2000; **68**: 550-557 [PMID: 10766881 DOI: 10.1136/jnnp.68.5.550]
  - 12 **Vernant JC**, Mauris L, Gessain A, Barin F, Gout O, Delaporte JM, Sanhadji K, Buisson G, de-Thé G. Endemic tropical spastic paraparesis associated with human T-lymphotropic virus type I: a clinical and seroepidemiological study of 25 cases. *Ann Neurol* 1987; **21**: 123-130 [PMID: 3030190 DOI: 10.1002/ana.410210204]
  - 13 **Morgan DJ**, Caskey MF, Abbehusen C, Oliveira-Filho J, Araujo C, Porto AF, Santos SB, Orge GO, Joia MJ, Muniz AL, Siqueira I, Glesby MJ, Carvalho E. Brain magnetic resonance imaging white matter lesions are frequent in HTLV-I carriers and do not discriminate from HAM/TSP. *AIDS Res Hum Retroviruses* 2007; **23**: 1499-1504 [PMID: 18160007 DOI: 10.1089/aid.2007.0077]
  - 14 **Yonenaga Y**, Arimura K, Suehara M, Arimura Y, Osame M. Electroencephalographic abnormalities in human T-cell lymphotropic virus type I-associated myelopathy. *Arch Neurol* 1989; **46**: 513-516 [PMID: 2712748 DOI: 10.1001/archneur.1989.00520410047022]
  - 15 **Castillo JL**, Cartier L, Araya F, Verdugo R, Mora C, Gibbs C. Evoked potential abnormalities in progressive spastic paraparesis associated to HTLV-1. *Acta Neurol Scand* 1991; **83**: 151-154 [PMID: 2031447 DOI: 10.1111/j.1600-0404.1991.tb04667.x]
  - 16 **Román GC**. Tropical myelopathies. *Handb Clin Neurol* 2014; **121**: 1521-1548 [PMID: 24365434 DOI: 10.1016/B978-0-7020-4088-7.00102-4]
  - 17 **Wu E**, Dickson DW, Jacobson S, Raine CS. Neuroaxonal dystrophy in HTLV-1-associated myelopathy/tropical spastic paraparesis: neuropathologic and neuroimmunologic correlations. *Acta Neuropathol* 1993; **86**: 224-235 [PMID: 8213080 DOI: 10.1007/BF00304136]
  - 18 **Kasai T**, Ikeda H, Tomaru U, Yamashita I, Ohya O, Morita K, Wakisaka A, Matsuoka E, Moritoyo T, Hashimoto K, Higuchi I, Izumo S, Osame M, Yoshiki T. A rat model of human T lymphocyte virus type I (HTLV-I) infection: in situ detection of HTLV-I provirus DNA in microglia/macrophages in affected spinal cords of rats with HTLV-I-induced chronic progressive myeloneuropathy. *Acta Neuropathol* 1999; **97**: 107-112 [PMID: 9928820 DOI: 10.1007/s004010050962]
  - 19 **Koyanagi Y**, Itoyama Y, Nakamura N, Takamatsu K, Kira J, Iwamasa T, Goto I, Yamamoto N. In vivo infection of human T-cell leukemia virus type I in non-T cells. *Virology* 1993; **196**: 25-33 [PMID: 8356797 DOI: 10.1006/viro.1993.1451]
  - 20 **Walter MJ**, Lehky TJ, Fox CH, Jacobson S. In situ PCR for the detection of HTLV-I in HAM/TSP patients. *Ann N Y Acad Sci* 1994; **724**: 404-413 [PMID: 8030966 DOI: 10.1111/j.1749-6632.1994.tb38939.x]
  - 21 **Lehky TJ**, Fox CH, Koenig S, Levin MC, Flerlage N, Izumo S, Sato E, Raine CS, Osame M, Jacobson S. Detection of human T-lymphotropic virus type I (HTLV-I) tax RNA in the central nervous system of HTLV-I-associated myelopathy/tropical spastic paraparesis patients by in situ hybridization. *Ann Neurol* 1995; **37**: 167-175 [PMID: 7847858 DOI: 10.1002/ana.410370206]
  - 22 **Hanon E**, Stinchcombe JC, Saito M, Asquith BE, Taylor GP, Tanaka Y, Weber JN, Griffiths GM, Bangham CR. Fratricide among CD8(+) T lymphocytes naturally infected with human T cell lymphotropic virus type I. *Immunity* 2000; **13**: 657-664 [PMID: 11114378 DOI: 10.1016/S1074-7613(00)00065-0]
  - 23 **Nagai M**, Brennan MB, Sakai JA, Mora CA, Jacobson S. CD8(+) T cells are an in vivo reservoir for human T-cell lymphotropic virus type I. *Blood* 2001; **98**: 1858-1861 [PMID: 11535522 DOI: 10.1182/blood.V98.6.1858]
  - 24 **Tsunetsugu-Yokota Y**, Terahara K. Receptor usage and the pathogenesis in acute and chronic virus infections. *Front Microbiol* 2012; **3**: 289 [PMID: 23024639 DOI: 10.3389/fmicb.2012.00289]
  - 25 **Cook LB**, Elemans M, Rowan AG, Asquith B. HTLV-I: persistence and pathogenesis. *Virology* 2013; **435**: 131-140 [PMID: 23217623 DOI: 10.1016/j.virol.2012.09.028]
  - 26 **Levin MC**, Rosenblum MK, Fox CH, Jacobson S. Localization of retrovirus in the central nervous system of a patient co-infected with HTLV-1 and HIV with HAM/TSP and HIV-associated dementia. *J Neurovirol* 2001; **7**: 61-65 [PMID: 11519484 DOI: 10.1080/135502801300069719]
  - 27 **Wrzesinski S**, Séguin R, Liu Y, Domville S, Planelles V, Massa P, Barker E, Antel J, Feuer G. HTLV type 1 Tax transduction in microglial cells and astrocytes by lentiviral vectors. *AIDS Res Hum Retroviruses* 2000; **16**: 1771-1776 [PMID: 11080825 DOI: 10.1089/08892220050193290]
  - 28 **Greten TF**, Slansky JE, Kubota R, Soldan SS, Jaffee EM, Leist TP, Pardoll DM, Jacobson S, Schneck JP. Direct visualization of antigen-specific T cells: HTLV-1 Tax11-19- specific CD8(+) T cells are activated in peripheral blood and accumulate in cerebrospinal fluid from HAM/TSP patients. *Proc Natl Acad Sci USA* 1998; **95**: 7568-7573 [PMID: 9636190 DOI: 10.1073/pnas.95.13.7568]
  - 29 **Höger TA**, Jacobson S, Kawanishi T, Kato T, Nishioka K, Yamamoto K. Accumulation of human T lymphotropic virus (HTLV)-I-specific T cell clones in HTLV-I-associated myelopathy/tropical spastic paraparesis patients. *J Immunol* 1997; **159**: 2042-2048 [PMID: 9257872]
  - 30 **Yamano Y**, Nagai M, Brennan M, Mora CA, Soldan SS, Tomaru U, Takenouchi N, Izumo S, Osame M, Jacobson S. Correlation of human T-cell lymphotropic virus type 1 (HTLV-1) mRNA with proviral DNA load, virus-specific CD8(+) T cells, and disease severity in HTLV-1-associated myelopathy (HAM/TSP). *Blood* 2002; **99**: 88-94 [PMID: 11756157 DOI: 10.1182/blood.V99.1.88]
  - 31 **Dhib-Jalbut S**, Hoffman PM, Yamabe T, Sun D, Xia J, Eisenberg H, Bergey G, Ruscetti FW. Extracellular human T-cell lymphotropic virus type I Tax protein induces cytokine production in adult human microglial cells. *Ann Neurol* 1994; **36**: 787-790 [PMID: 7979225 DOI: 10.1002/ana.410360516]
  - 32 **Yoshida M**. Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. *Annu Rev Immunol* 2001; **19**: 475-496 [PMID: 11244044 DOI: 10.1146/annurev.immunol.19.1.475]
  - 33 **Gillet NA**, Malani N, Melamed A, Gormley N, Carter R, Bentley D, Berry C, Bushman FD, Taylor GP, Bangham CR. The host genomic environment of the provirus determines the abundance of HTLV-1-infected T-cell clones. *Blood* 2011; **117**: 3113-3122 [PMID: 21228324 DOI: 10.1182/blood-2010-10-312926]
  - 34 **Endo K**, Tsukamoto T. Experimental bystander encephalitis induced by immunization with HTLV-I-producing T cells in mice. *Acta Neurol Scand* 1997; **96**: 106-113 [PMID: 9272187 DOI: 10.1111/j.1600-0404.1997.tb00249.x]
  - 35 **Ishiguro N**, Abe M, Seto K, Sakurai H, Ikeda H, Wakisaka A, Togashi T, Tateno M, Yoshiki T. A rat model of human T lymphocyte virus type I (HTLV-I) infection. I. Humoral antibody response, provirus integration, and HTLV-I-associated myelopathy/tropical spastic paraparesis-like myelopathy in seronegative HTLV-I carrier rats. *J Exp Med* 1992; **176**: 981-989 [PMID: 1402668 DOI: 10.1084/jem.176.4.981]
  - 36 **Yoshiki T**. Chronic progressive myeloneuropathy in WKAH rats induced by HTLV-I infection as an animal model for HAM/TSP in humans. *Intervirology* 1995; **38**: 229-237 [PMID: 8682621]

- 37 **Tomaru U**, Ikeda H, Ohya O, Abe M, Kasai T, Yamasita I, Morita K, Wakisaka A, Yoshiki T. Human T lymphocyte virus type I-induced myeloneuropathy in rats: implication of local activation of the pX and tumor necrosis factor-alpha genes in pathogenesis. *J Infect Dis* 1996; **174**: 318-323 [PMID: 8699061 DOI: 10.1093/infdis/174.2.318]
- 38 **Tomaru U**, Ikeda H, Jiang X, Ohya O, Yoshiki T. Provirus expansion and deregulation of apoptosis-related genes in the spinal cord of a rat model for human T-lymphocyte virus type I-associated myeloneuropathy. *J Neurovirol* 2003; **9**: 530-538 [PMID: 13129767 DOI: 10.1080/713831646]
- 39 **Kushida S**, Matsumura M, Tanaka H, Ami Y, Hori M, Kobayashi M, Uchida K, Yagami K, Kameyama T, Yoshizawa T. HTLV-1-associated myelopathy/tropical spastic paraparesis-like rats by intravenous injection of HTLV-1-producing rabbit or human T-cell line into adult WKA rats. *Jpn J Cancer Res* 1993; **84**: 831-833 [PMID: 8407544 DOI: 10.1111/j.1349-7006.1993.tb02052.x]
- 40 **Miyatake Y**, Ikeda H, Ishizu A, Baba T, Ichihashi T, Suzuki A, Tomaru U, Kasahara M, Yoshiki T. Role of neuronal interferon-gamma in the development of myelopathy in rats infected with human T-cell leukemia virus type I. *Am J Pathol* 2006; **169**: 189-199 [PMID: 16816372 DOI: 10.2353/ajpath.2006.051225]
- 41 **Câmara CC**, Oriá RB, Felismino TC, da Silva AP, da Silva MA, Alcântara JV, Costa SB, Vicente AC, Teixeira-Santos TJ, de Castro-Costa CM. Motor behavioral abnormalities and histopathological findings of Wistar rats inoculated with HTLV-1-infected MT2 cells. *Braz J Med Biol Res* 2010; **43**: 657-662 [PMID: 20521016 DOI: 10.1590/S0100-879X2010007500050]
- 42 **De Castro-Costa CM**. [Tropical spastic paraparesis: a necessary redefinition]. *Arq Neuropsiquiatr* 1996; **54**: 131-135 [PMID: 8736159]
- 43 **Ruddle NH**, Li CB, Horne WC, Santiago P, Troiano N, Jay G, Horowitz M, Baron R. Mice transgenic for HTLV-I LTR-tax exhibit tax expression in bone, skeletal alterations, and high bone turnover. *Virology* 1993; **197**: 196-204 [PMID: 8212554 DOI: 10.1006/viro.1993.1580]
- 44 **Beilke MA**, Traina-Dorge V, England JD, Blanchard JL. Polymyositis, arthritis, and uveitis in a macaque experimentally infected with human T lymphotropic virus type I. *Arthritis Rheum* 1996; **39**: 610-615 [PMID: 8630109 DOI: 10.1002/art.1780390410]
- 45 **Akagi T**, Yoshino T, Motoi M, Takata H, Yano S, Miyoshi I, Oka T, Ohtsuki Y. Isolation of virus-producing transformants from human gastric cancer cell line, HGC-27, infected with human T-cell leukemia virus type I. *Jpn J Cancer Res* 1988; **79**: 836-842 [PMID: 3139597 DOI: 10.1111/j.1349-7006.1988.tb00045.x]
- 46 **Louboutin JP**, Agrawal L, Reyes BA, Van Bockstaele EJ, Strayer DS. Protecting neurons from HIV-1 gp120-induced oxidant stress using both localized intracerebral and generalized intraventricular administration of antioxidant enzymes delivered by SV40-derived vectors. *Gene Ther* 2007; **14**: 1650-1661 [PMID: 17914406 DOI: 10.1038/sj.gt.3303030]
- 47 **Louboutin JP**, Reyes BA, Agrawal L, Van Bockstaele EJ, Strayer DS. Intracisternal rSV40 administration provides effective pan-CNS transgene expression. *Gene Ther* 2012; **19**: 114-118 [PMID: 21614027 DOI: 10.1038/gt.2011.75]
- 48 **Louboutin JP**, Chekmasova AA, Marusich E, Chowdhury JR, Strayer DS. Efficient CNS gene delivery by intravenous injection. *Nat Methods* 2010; **7**: 905-907 [PMID: 20953176 DOI: 10.1038/nmeth.1518]
- 49 **Araujo AQ**, Silva MT. The HTLV-1 neurological complex. *Lancet Neurol* 2006; **5**: 1068-1076 [PMID: 17110288 DOI: 10.1016/S1474-4422(06)70628-7]

P- Reviewer: Juan DS, Sotelo J

S- Editor: Tian YL L- Editor: A E- Editor: Jiao XK





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

