تظاهرات نورولوژیک HTLV-1

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تاریخچه

- ویروس htlv-1را اولین بار در سال ۱۹۸۰توسط اقای گالو وهمکارانش بعنوان رترو ویروس نوع c در یک رده T لنفوسیتوییید درنوعی لنفوم جلدی شناسایی کردند.
- در ایران ویروس htlv-1نخستین بار در جمعیت یهودی که از مشهد مهاجرت کرده و در اسراییل سکونت داشتند شناسایی شد .
- در سال ۱۹۸۵ اولین بار پروفسور دوته و دکتر جسن از انیستوپاستور پاریس ارتباط htlv-1ودرگیری نخاعی در یک بیمار مبتلا به پاراپارزی اسپاستیک از مارتنیک اثبات نمود
- چند ماه بعد اسامه از ژاپن در مقاله ای تحت عنوان میلوپاتی همراه با htlv-1 HAMدر مجله لنتست چاپ شد.
- در سال ۱۹۸۸ گروهی از سازمان بهداشت جهانی در نشستی که در کاگوشیمای ژاپن داشتند. بیماری TSP و HAM را تحت عنوان پدیده واحد بنام HAM/TSP نامگذادی کردند.

EPIDEMIOLOGY of HTLV-1 in IRAN

- In 1992 (1370) WHO presented IRAN (Khorasan) as an endemic region of HTLV-1
- HTLV-1 is more common in the north of Khorasan province especially Neyshabour, Mashad and Ghoochan
- Why Khorasan?

PATHOGENESIS

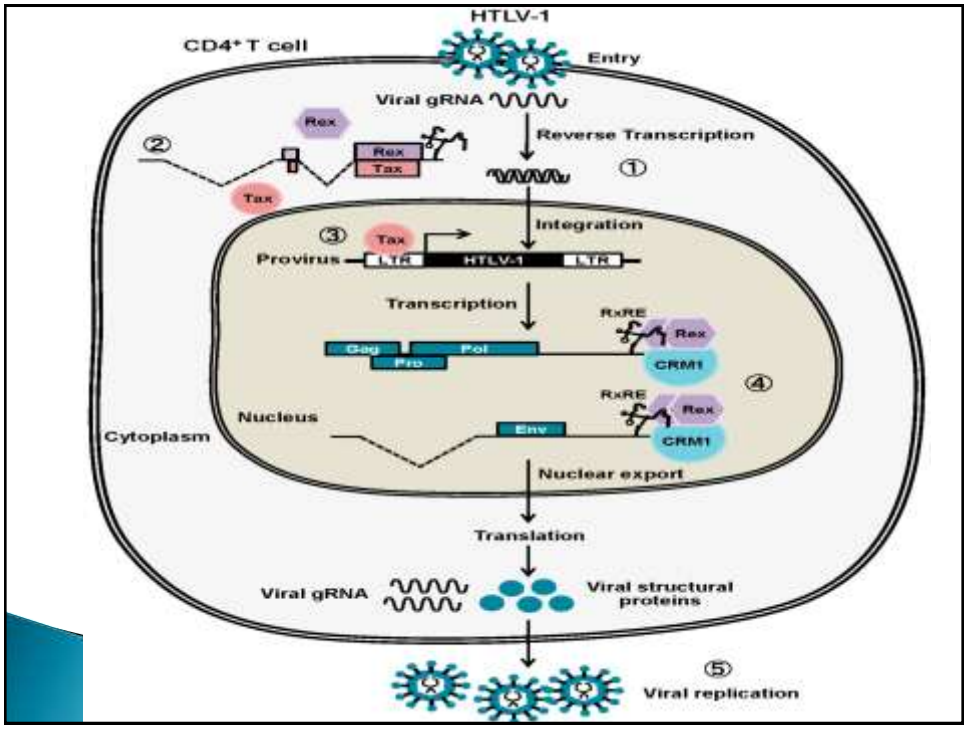
- Direct attack of virus to the neurons is not proved
- Indirect contamination of nervous system by lymphocytes
- Autoimmune mechanisms (humeral and cellular) is suspected
- ***Main pathology is demyelination***

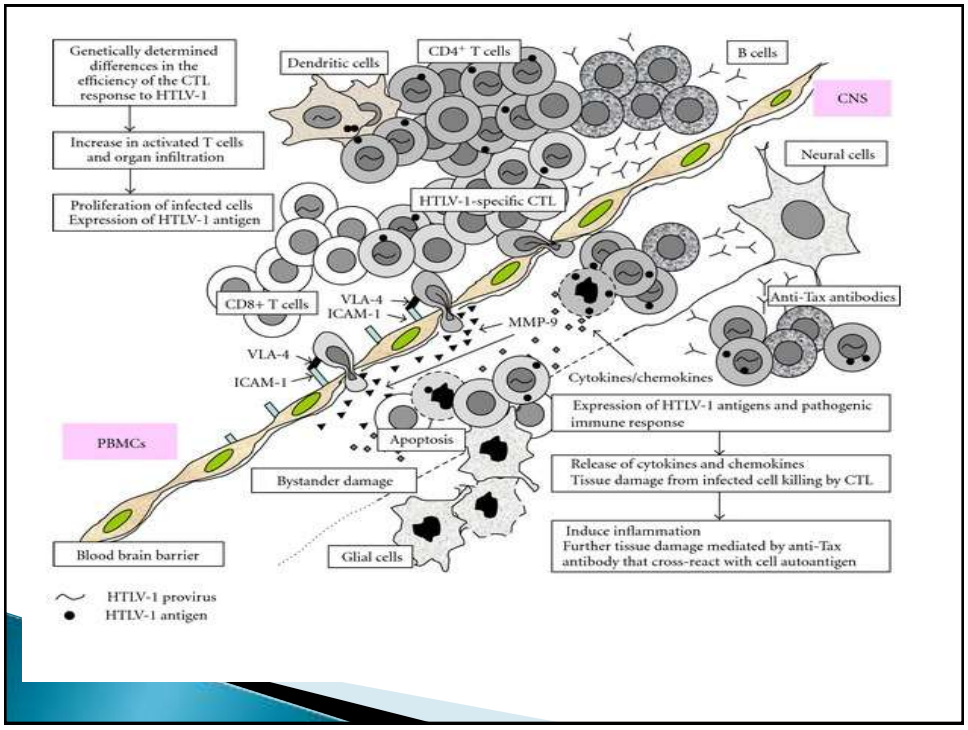
Virology

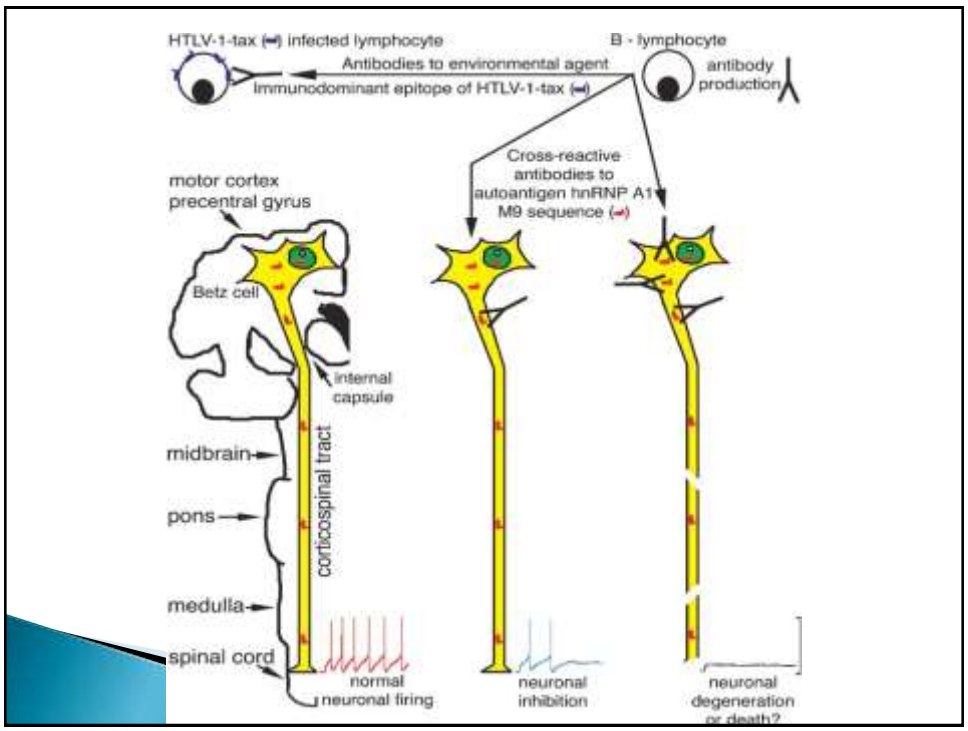
HTLV-1 is an enveloped, double-stranded RNA type C retrovirus. During the life cycle of the virus the RNA is converted to double-stranded DNA and integrated into the DNA of the host cell. This integrated DNA is referred to as the 'provirus'.

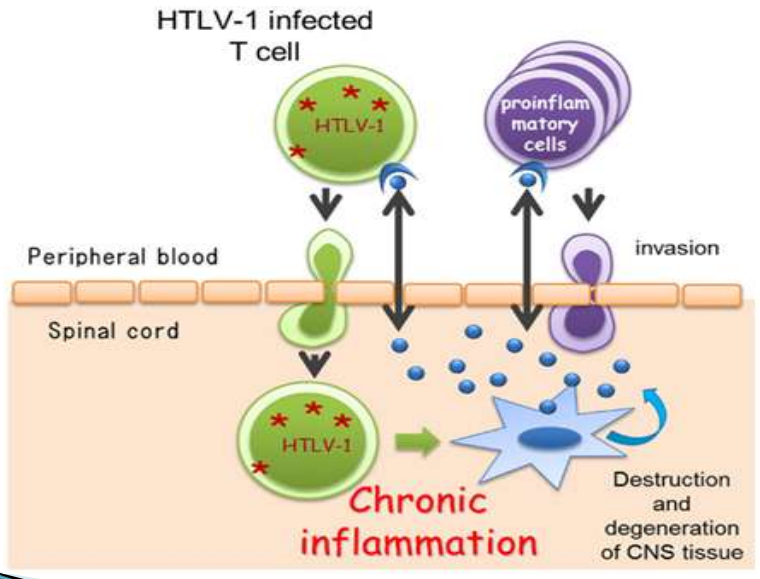
HTLV-1 exists largely as a cell-associated provirus and is transmitted from cell to cell via a viral synapse. This process may explain the lack of infection associated with plasma.

Provirus loads vary between individuals by more than 10 000 fold but within an infected individual the provirus load varies little over time.




Genetically determined differences in the efficiency of the CTL response to HTLV-1
Increase in activated T cells and organ infiltration
Proliferation of infected cells Expression of HTLV-1 antigen
Dendritic cells
CD4+ T cells
B cells
CNS
Neural cells
HTLV-1-specific CTL
CD8+ T cells
VLA-4
ICAM-1
MMP-9
Anti-Tax antibodies
VLA-4
ICAM-1
Cytokines/chemokines
Expression of HTLV-1 antigens and pathogenic immune response
PBMCs
Apoptosis
Release of cytokines and chemokines Tissue damage from infected cell killing by CTL
Bystander damage
Induce inflammation Further tissue damage mediated by anti-Tax antibody that cross-react with cell autoantigen
Blood brain barrier
Glial cells
HTLV-1 provirus
HTLV-1 antigen


HTLV-1-tax (➡) infected lymphocyte
B - lymphocyte
Antibodies to environmental agent
Immunodominant epitope of HTLV-1-tax (➡)
antibody production
Cross-reactive antibodies to autoantigen hnRNP A1 M9 sequence (➡)
motor cortex precentral gyrus
Betz cell
internal capsule
midbrain
pons
medulla
spinal cord
corticospinal tract
normal neuronal firing
neuronal inhibition
neuronal degeneration or death?



The Global Spread of HTLV-1 Infection I

HTLV-1 is an ancient virus which has infected humans for thousands of years. The simian counter-part (STLV-1) is genetically almost identical.

HTLV-1 Origins

- HTLV-1 is thought to have originated in Africa and spread with human migration (including migration across the Berring land bidge)
- Thus, the virus is endemic in "older" indigenous populations including many Amerindian peoples of both North and South America, the populations of Northern and South-western Japan (rather than Korea and central Japan) and Melanesian (migration more than 5,000 years).
- Post-Colombian migrations took HTLV-1 to the Caribbean and the Americas (for a second time) and latterly to Europe
- The origin of HTLV-1 in Romania is unknown.

Prevalence

- The prevalence of the infection seems to decline in subsequent generations migrating from endemic to non-endemic areas (cultural changes related particularly to breastfeeding may be important here).
- Although both HTLV-1 and HIV-1 have similar transmission routes, in some areas their prevalence trends are divergent – HTLV-1 declining and HIV-1 increasing.

Who is at Risk of Acquiring HTLV-1 Infection?

An estimated 15-25 million individuals worldwide are infected with HTLV-1 [3]. The infection is endemic in regions of Japan, sub-Saharan Africa, the Americas, Melanesia (north of Australia, including Fiji and New Guinea) and the Middle East.

HTLV-1 infection remains uncommon in the general population in Europe with the exception of Romania. Nonetheless, it is considerably more common among immigrants from endemic areas, their sexual partners and offspring. Increased risk has been reported amongst sex workers and (for HTLV-2) injecting drug users.

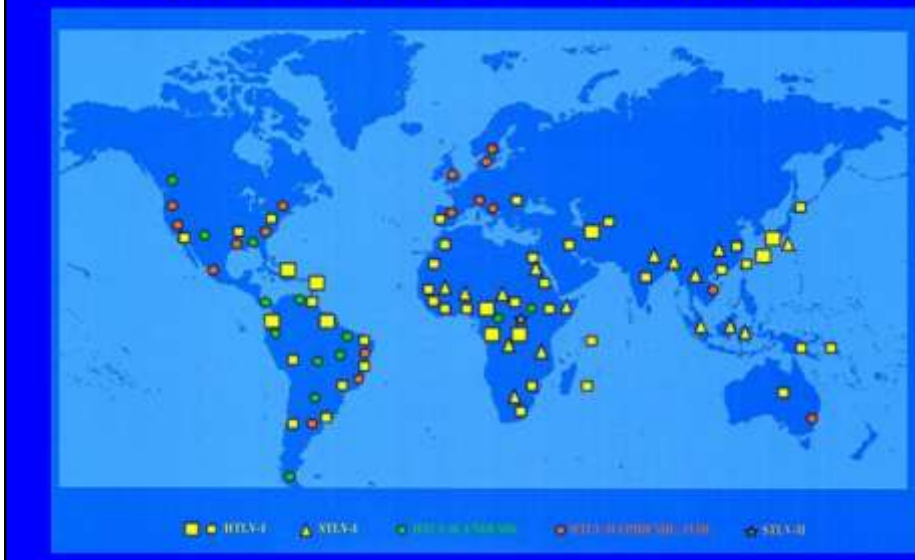
Epidemiological studies in indigenous Europeans (except Romania) usually implicate transmission through sexual intercourse with partners from endemic regions or blood transfusion. The seroprevalence among low-risk populations in Europe is less than 0.1%.

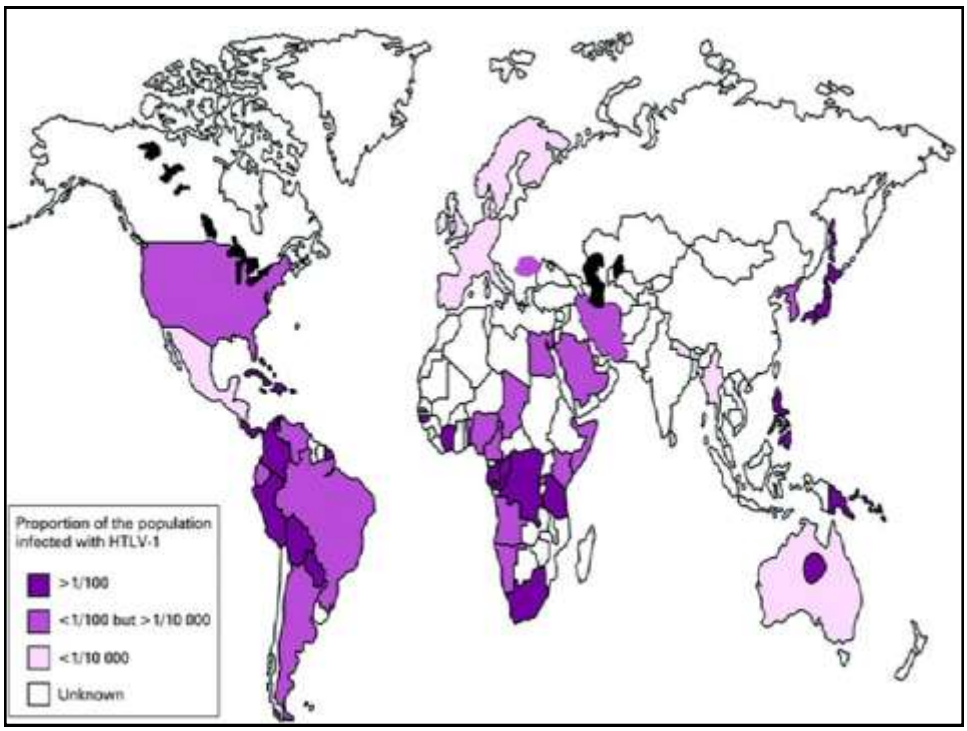
An estimated 20,000 people in the UK are infected with HTLV-1 [4].

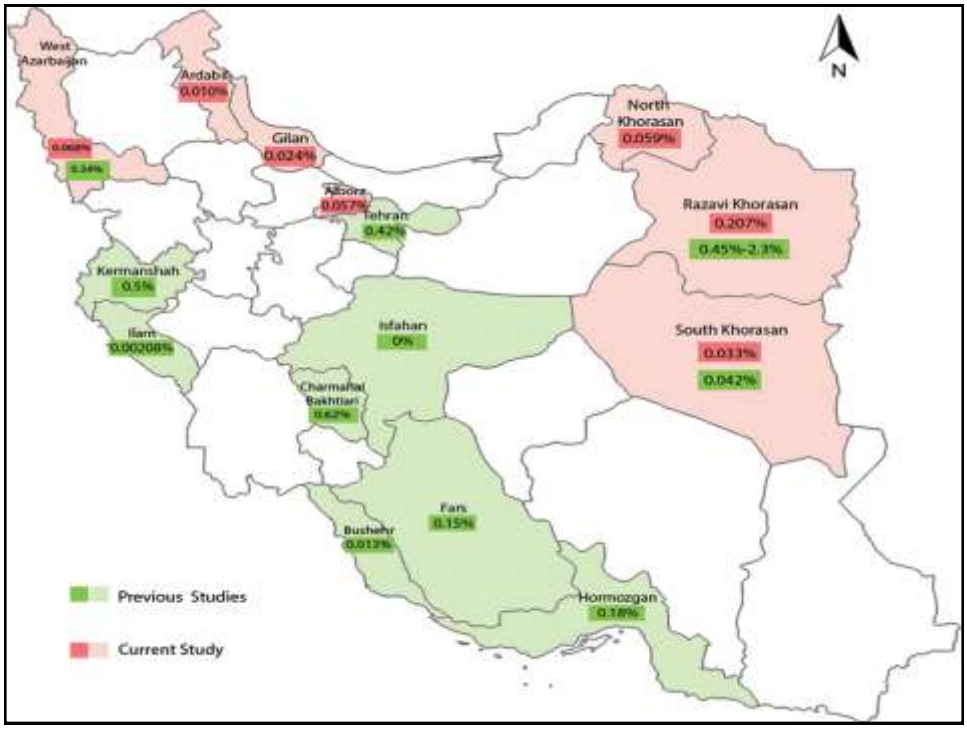
HTLV-1 HISTORY

- HTLV1 recognized for first time in a 28 Y/O black man with ATL in 1980
- Gessain and De The described a form of myelopathy caused by HTLV1 in a patient from Martinique in 1985
- Tropical Spastic Paraparesis (TSP)
- HTLV1 Associated Myelopathy (HAM)
- HAM/TSP
- HTLV1 is a RNA virus of Retroviridea family

EPIDEMIOLOGY of HTLV-1&2







EPIDEMIOLOGY of HTLV-1

- Prevalence of seropositivity is different:
  south of Japan 10-30%
  Africa 1-9%
  Caribbean islands ... 1-7%
  Neyshabour 3%
  Mashhad 1.3-2.6%
- Only 1-5% of healthy carriers lead to HAM
- Incubation period: 6 months to 3 years
- Mean age of onset: 30 y/o (4th decade)
- F to M ratio :3/1 to 2/1

TRANSMISSION

- Sexual contacts :M to F is more common than F to M (60/1)
- Blood transfusion especially cell containing products
- Perinatal
- Breast feeding
- I.V Drug abuse

Transmission of HTLV-1 I

The three major modes of transmission of HTLV-1 are:

1. Perinatal
   - Especially via prolonged breastfeeding – the risk of vertical transmission (15-25%) is largely attributable to breastfeeding with less than 5% occurring in utero or during birth [1].
2. Sexual
   - Higher risk from male to female
3. Exposure to infected lymphoid cells
   - For example by blood transfusion, needle-stick injuries or needle sharing by injected drug users.
   - Transfusion of infected blood products leads to seroconversion in 40-85% of recipients (with immune suppression at the time of transfusion an important risk factor).
   - Organ transplantation (kidney and liver) has also resulted in transmission.

Transmission of HTLV-1 III

The latent period can be many decades (e.g. peak onset of ATLL *(Adult T cell Leukaemia/lymphoma)* in Japan is in the 6th and 7th decades) but much shorter periods (months) have been described after acquisition through blood transfusion.

Universal screening of blood donors for HTLV-1 was introduced in the UK in 2002. The screening test also detects HTLV-2.

HTLV-2

This retrovirus is endemic amongst injecting drug users in North America and Europe. Its role in the development of disease however is uncertain.

The prevalence of HTLV-2 in the UK is significantly less than HTLV-1. Most HTLV-2 infected blood donors have no history of IDU *(Intravenous Drug Use)* and have probably acquired infection through sexual intercourse.

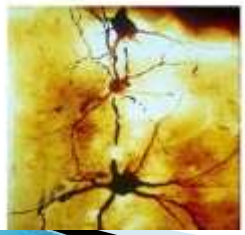
HTLV-2 is transmitted from mother to child, predominantly through breast-feeding.

Risk Factors for Developing HTLV-1 associated Disease

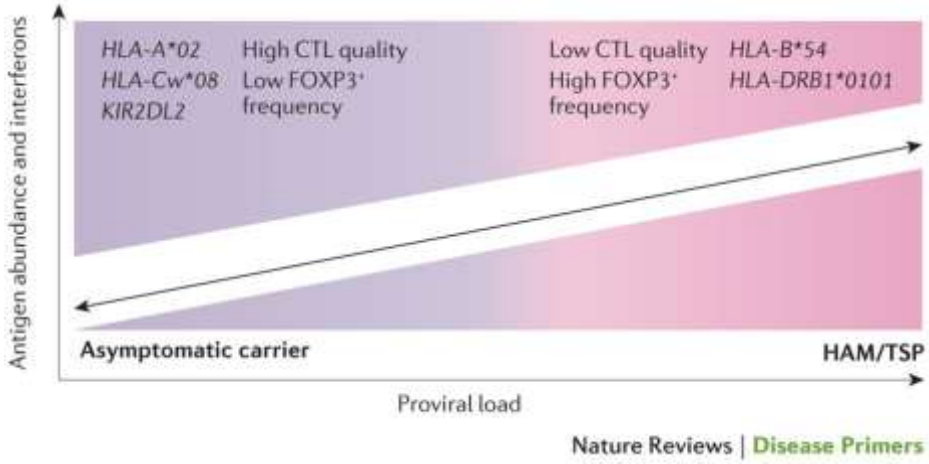
HTLV-1 causes a lifelong infection but, in contrast to HIV-1, most of those infected remain asymptomatic throughout life.

The lifetime risk of a HTLV-1 carrier developing the most common neurological complication – a spastic paraparesis (known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP))- is 0.25% in Japan and approximately 3% elsewhere [5].

HTLV-1 infection is also associated with a lifetime risk of 2-6% of adult T-cell leukaemia/lymphoma [5].



Spinal motorneurons. Image courtesy of Welcome Images.



Risk Factors for Developing HAM/TSP

When to suspect HTLV-I myelopathy in a non-endemic country	
1. Clinical features compatible with HTLV-I myelopathy	• A slowly progressive, symmetrical spastic paraparesis • Neurogenic bladder symptoms • Sensory symptoms +/- low back pain
2. Risk factors for the acquisition of HTLV-I	• Born in an endemic country • Having a sexual partner from an endemic country • Being the offspring of someone from an endemic country

A high HTLV-1 provirus load is associated with the development of HAM/TSP. HAM/TSP is rarely seen in patients with viral load <1% [1 infected cell /100 PBMCs (Peripheral blood mononuclear cells)].

Acquisition of infection in adult life is associated with the development of HAM/TSP. Some evidence suggests that an earlier age of sexual intercourse and more than five lifetime sexual partners is associated with developing HAM/TSP [6].

Sexually acquired HTLV-1 is the most common transmission factor for the development of HAM/TSP, despite the fact that acquiring HTLV-1 through blood transfusion is associated with the highest viral inoculum. However transfusion/transplantation during immune suppression has resulted in rapid development and progression of HAM/TSP.

Risk Factors for Developing HAM/TSP

Gender and Progression

More women than men develop HAM/TSP (a difference not entirely attributable to the higher prevalence amongst women in endemic areas) and the disease progresses faster in women. In the UK nearly 80% of patients with HAM/TSP at the National Centre for Human Retrovirology are women.

The peak incidence of HAM/TSP is in the 4th and 5th decades.
A few patients progress more rapidly, particularly those aged more than 50 years at onset (or children), with a high provirus load and high antibody titres. A subacute presentation, leading to severe paraplegia in less than 2 years has been described in post-transfusional and post-transplant cases [7].

Image copyright Ferdinand Reus.

HTLV-1 NEUROLOGICAL COMPLICATIONS

- Myelopathy
- Polyneuropathy
- ALS like syndrome
- Cerebellar ataxia
- Cranial neuropathy
- Dementia
- Myositis
- MS like presentation (rare)

Neurological Complications of HTLV-1 Infection

Spastic paraparesis has been reported in the tropics for many years. The association with HTLV-1 was first recognised in 1985. Other complications can be divided into:

Other neurological complications

Other neurological complications reported (some in isolated case reports only) in association with HTLV-1 infection include…

- Myositis
- Cognitive impairment
- Encephalitis/ encephalopathy
- Small-fibre sensory polyneuropathy
- Autonomic dysfunction
- Motor neuron disease/ amyotrophic lateral sclerosis

Other non-neurological conditions

Other non-neurological conditions reported in association with HTLV-1 infection include…

- Uveitis
- Sjorgren's syndrome
- Pneumonitis
- Infective dermatitis
- Strongyloides stercoralis hyperinfection
- arthropathy
- thyroiditis
- crusted scabies
- leprosy

The best quality evidence exists to link adult T-cell leukaemia/lymphoma (ATLL), HAM/TSP and uveitis with HTLV-1 infection.

SIGN & SYMPTOMS of HAM/TSP

- Motor weakness (spastic paraparesis)
- Sensory disturbances (paresthesia)
- Sensory ataxia
- Bladder dysfunction (spastic bladder)
- Bowl dysfunction
- Impotence
- Pain

Motor Disturbance

Symptoms: gait disturbance, tendency to fall, stumbling, and leg weakness

Signs: spastic paraparesis, weakness and hyperreflexia of the lower limbs, clonus, and Babinski's sign

Sensory Disturbance

Symptoms: pain and numbness at the lumbar level and lower limbs and back pain

Signs: paresthesia of the feet and occasionally of the hands, sensory level at the lower thoracic spinal cord, loss of light touch sensation

Autonomic Dysfunction

Symptoms: urinary frequency, urgency, incontinence, retention, constipation, and sexual dysfunction

Signs: neurogenic bladder, overactive bladder, diminished peristalsis, and erectile dysfunction

Clinical Features of HAM/TSP I

Symptoms

The symptoms usually begin in adulthood, most frequently after the age of 30. HAM/TSP usually presents as a slowly progressive spastic paraparesis. A minority (11% in UK cohort) appear to have a non-progressive illness [4].

Weakness of the legs

- In 60%, this is the first symptom and may be unilateral initially.

Symptom onset and age

- The median age from symptom onset to unilateral walking aid is 6 years, bilateral walking aid 13 years and wheelchair dependence 21 years [8]. In a UK cohort a 10m timed walk deteriorated by a mean of 2s/10m/yr amongst those not using a walking aid [4].

Bladder

- Bladder symptoms are very common and may precede the paraparesis by some years.

Pain

- Present in about 50%, usually in the lumbar region and often radiating to the legs. It is commonly severe and more distressing than the gait symptoms

Sensory disturbance

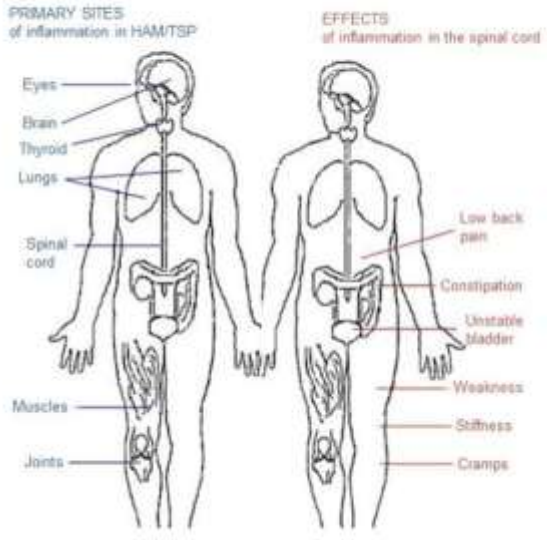
- Sensory disturbance other than pain is generally mild although there may be paraesthesia of the feet and occasionally the hands.

Clinical Features of HAM/TSP II

Signs include:

- The cranial nerves are typically unaffected
- Patients have a spastic paraparesis with weakness of the lower limbs most evidently proximally
- There is often diffuse hyper-reflexia and extensor plantar responses
- Ankle jerks however may be absent (possibly representing additional peripheral nervous system involvement)
- Upper limb strength is usually preserved
- A sensory level is unusual. There is often a discrepancy between striking motor signs and a mild sensory component

Clinical Features of HAM/TSP III



DIAGNOSIS

- SEROLOGICAL TESTS (blood & CSF):
  ELISA
  Western Blot
- Polymeras Chain Reaction (PCR)
- ***MRI (usually normal)***
- EMG/NCV

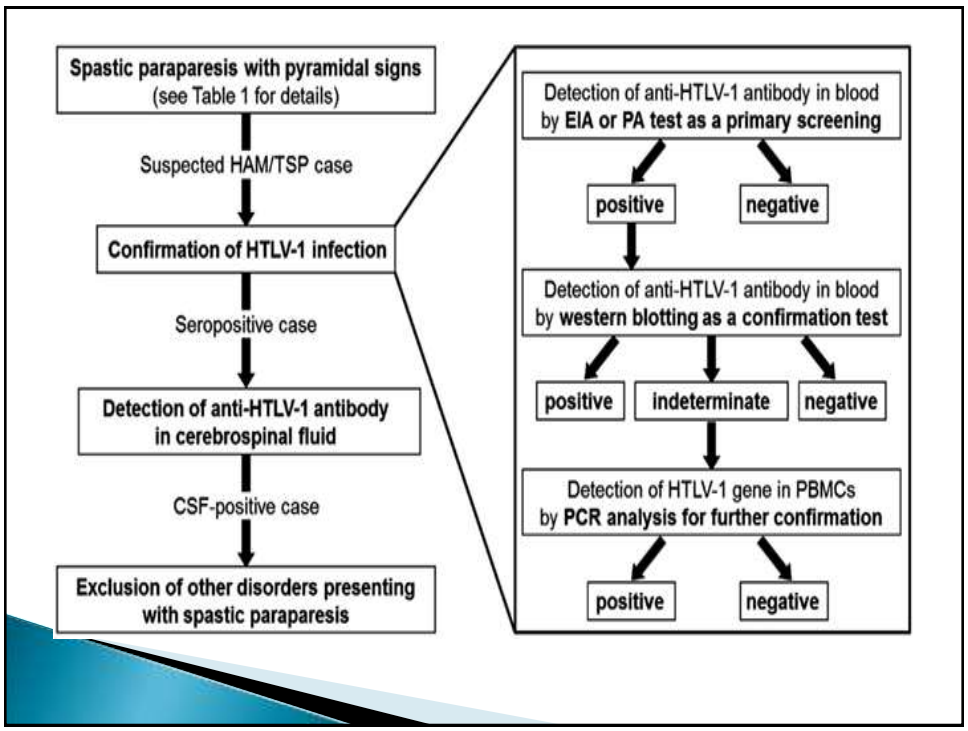


Table 2. World Health Organization diagnostic criteria for HAM/TSP.

Age and sex incidence	Mostly sporadic and adult, but sometimes familial; occasionally seen in childhood; females predominant
Onset	Usually insidious but may be sudden
Main neurological manifestations	Chronic spastic paraparesis, which usually progresses slowly, sometimes remaining static after initial progression Weakness of the lower limbs, more marked proximally Bladder disturbance usually an early feature; constipation usually occurs later; impotence or decreased libido is common Sensory symptoms such as tingling, pins and needles, and burning are more prominent than objective physical signs Low lumbar pain with radiation to the legs is common Vibration sense is frequently impaired; proprioception is less often affected Hyperreflexia of the lower limbs, often with clonus and Babinski's sign Hyperreflexia of the upper limbs, positive Hoffman's and Tromner signs frequent; weakness may be absent Exaggerated jaw jerk in some patients
Less frequent neurological findings	Cerebellar signs, optic atrophy, deafness, nystagmus, other cranial nerve deficits, hand tremor, absent, or decreased ankle jerk. Convulsions, cognitive impairment, dementia, or impaired consciousness are rare Muscular atrophy, fasciculations (rare), polymyositis, peripheral neuropathy, polyradiculopathy, cranial neuropathy, meningitis, encephalopathy
Systemic non-neurological manifestations	Pulmonary alveolitis, uveitis, Sjogren's syndrome, arthropathy, vasculitis, ichthyosis, cryoglobulinemia, monoclonal gammopathy, adult T cell leukemia/lymphoma
Laboratory diagnosis	Presence of HTLV-1 antibodies or antigens in blood and CSF CFS may show mild lymphocyte pleiocytosis Lobulated lymphocytes may be present in blood and/or CSF Mild to moderate increase of protein may present in CSF

CSF, cerebrospinal fluid.

Diagnostic Tests used to Detect HTLV-1

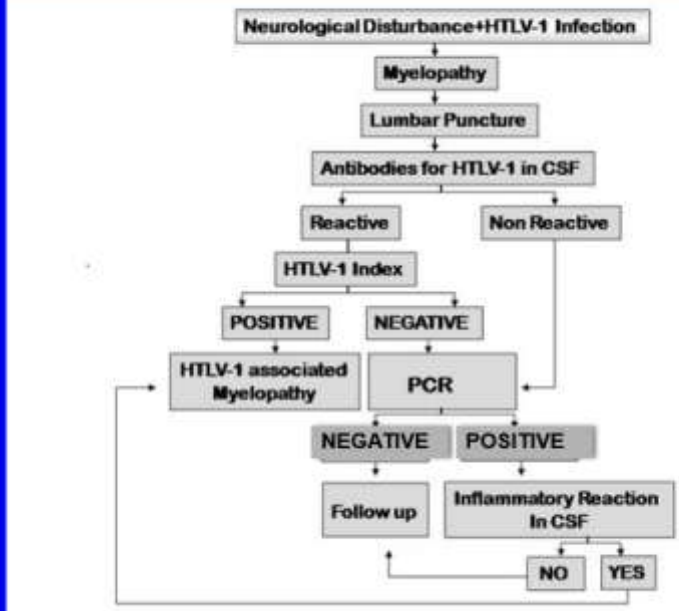
Blood

- Serological screening for HTLV-1 is by an enzyme immunoassay (EIA) or particle agglutination test
- Confirmatory testing of EIA positive results is essential to eliminate false positives and distinguish between HTLV-1 and HTLV-2 (HTLV-2 may have a role in the development of disease but this is less certain)
- A western blot is the preferred serological confirmatory test as this also types the infection. HTLV-1 DNA PCR on a blood sample is required if the western blot is indeterminate
- Proviral load which is a useful prognostic marker is determined by quantitative PCR

CSF

- There may be a mild CSF pleocytosis (usually less than 50 cells/mm^3) and a mild to moderately increased CSF protein
- Antibodies against HTLV-1 are found in the CSF in higher levels in patients with HAM/TSP than in asymptomatic carriers
- The HTLV-1 provirus can be demonstrated in the CSF of HAM/TSP patients by PCR
- Measuring the provirus in blood and CSF simultaneously helps to confirm a diagnosis of HAM/TSP as the ratio of proviral load in CSF to that in peripheral blood is above 1.0 in those with HAM/TSP

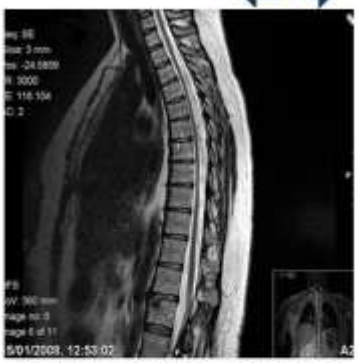
DIAGNOSIS of HAM/TSP



The Role of Neuroimaging in the Diagnosis of HAM/TSP

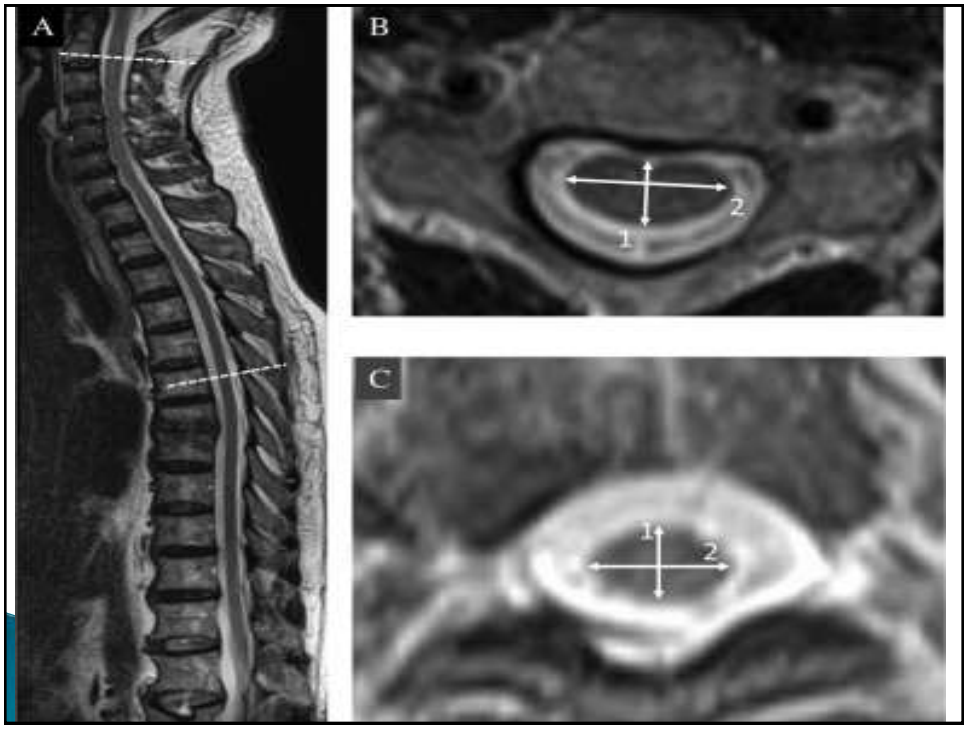
Non-specific periventricular and subcortical white matter lesions have been observed in 50-80% of patients with HAM/TSP on brain MRI [9,10]. However, these lesions do not distinguish HAM/TSP patients from asymptomatic HTLV-1 carriers and there have not been sufficient comparisons with HTLV-1 negative controls.

Spinal cord atrophy has been observed with MRI in a minority of patients (14% in one small series) [9].



An MRI scan of the thoracic spine shows some spinal cord atrophy.

Spinal cord swelling or high-signal intensity in the posterior columns has also been observed, possibly reflecting early, active spinal cord inflammation


A
B
2
1
C
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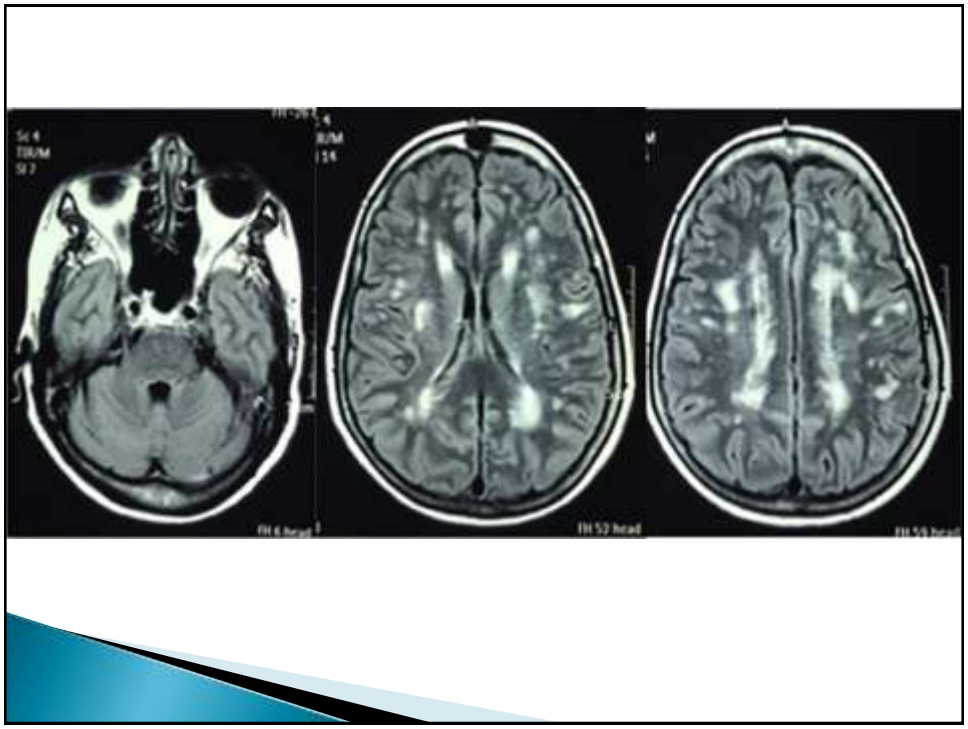


TREATMENT

- Symptomatic Tx:
  - Antispastic agents
  - Anticholinergic agents
  - Physiotherapy
- Etiological Tx:
  - Corticosteroids
  - Cytotoxics
  - Alpha Interferon
  - Other Immunomodulators

Current Management Approaches in HTLV-1 Associated Neurological Disease II

Symptomatic management of HAM/TS

- Antispasmodics, laxatives and management of bladder and erectile dysfunction are all important facets of the symptomatic management of HAM/TSP.
- Physiotherapy is useful to maximise function.
- Urinary tract infections are common and often result in transient neurological deterioration, therefore recognition and prompt treatment is vital.

Current Management Approaches in HTLV-1 Associated Neurological Disease I

In practice, steroids are often used despite the poor evidence base. This probably reflects the premise that there is a significant inflammatory phase early in the illness.

1g of IV methylprednisolone is often used (usually for three days) to improve symptoms generally, especially pain. The effect of steroids is generally transient, lasting weeks to months and subsequent treatments are very often less effective.

Ciclosporin

- In early (<2 years from onset) disease, ciclosporin is now used in the UK based on the results from as yet unpublished work from the National Centre for Human Retrovirology
- If this is not tolerated then methotrexate us an alternative (based on anecdotal evidence only)
- Early and more aggressive management is now often favoured, although more studies are needed.

Pain management

- Pain management required careful attention as pain is commonly of multiple aetiologies.

Randomised Controlled Trials in HAM/TSP

Interferon alpha has been shown to be of some short term benefit, of varying degrees in a dose ranging study [11].

Zidovudine plus Lamivudine showed no clinical benefit compared to placebo [12].

The results from studies at the National Centre for Human Retrovirology at St Mary's Hospital, Paddington of Infliximab and Cyclosporin as potential therapeutic agents in HAM/TSP are in preparation. The Centre is keen and is commissioned to see all UK patients (except from Wales) with HTLV-1.

Other studies

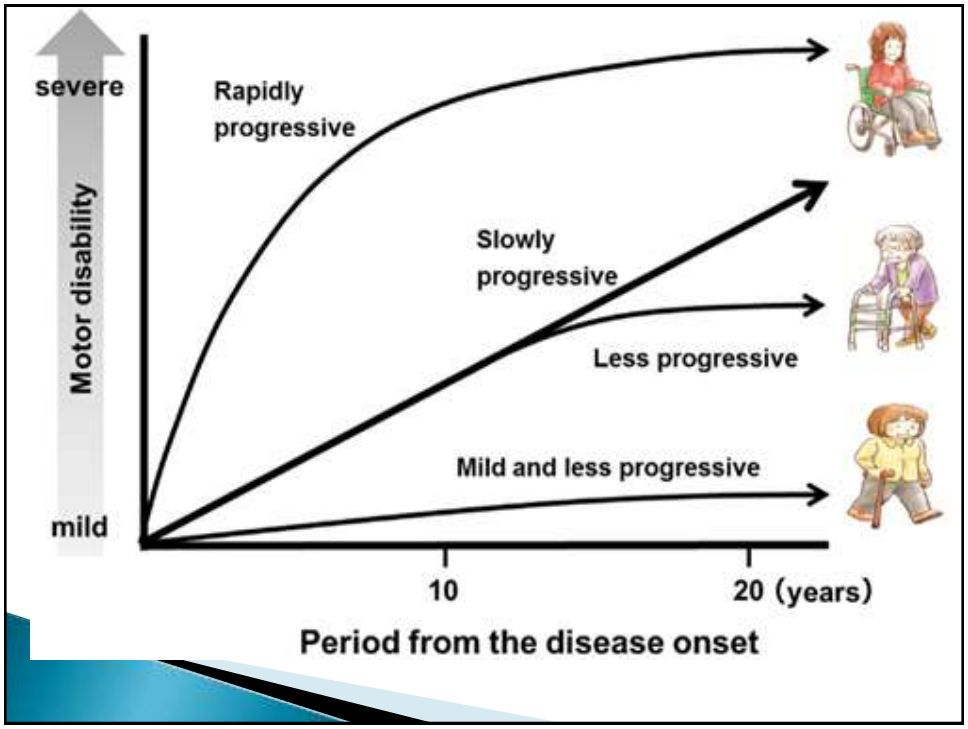
- Multiple small observational studies of a variety of agents have been published with limited evidence of benefit
- Plasmapheresis has shown some improvements in gait and sensory disturbance in small, uncontrolled studies only.

Interferon alpha. Image courtesy of Nelvit Dilmen.

Authors	Country	Study design	Reagents	Treatment regimen	Study period	No. of patients	Rate of Efficacy	Note
Osame et al. (1990b)	Japan	Open-label	Prednisolone	60–80 mg qod for 2 month → 10 mg qd/month for 6 month → 5 mg qod for 3 month	11 Month	65	90.8% (59/65) 56.9% (>1)	Incidence of side effects: 20% (13/6
Costa et al. (2008)	Brazil	Case series	Methylprednisolone	1 g × 3 days/month for 3–4 month	2.2 Years	39	24.5%	Transient effect
Nakagawa et al. (1996)	Japan	Open-label	Prednisolone	1–2 mg/kg qd or qod for 1–2 month → tapering	6–12 Month	131	81.7% 69.5% (>1)	Decrease of CSF neopterin
			Methylprednisolone	500 mg–1 g × 3 days		10	30.0%	For rapid progression
			Interferon-α	3 MU/day × 30 days	1–3 Month	32	62.5% 21.9% (>1)	Transient effect Incidence of side effects: 65.6% (21
Martin et al. (2012)	UK	Open-label	Cyclosporine A	2.5–5 mg/kg/day bd for 48 week	72 Week	7	71.4% (5/7) after 3 Month	Clinical failure: two patients
Izumo et al. (1996)	Japan	Multicenter double-blind RCT	Interferon-α	0.3 MU/day × 28 days 1 MU/day × 28 days 3 MU/day × 28 days	8 Week	15 17 16	7.1% 23.5% 66.7%	Incidence of side effects: 26.7% (4/ 29.4% (5/17) 50.0% (8/16)
Yamasaki et al. (1997)	Japan	Case series	Interferon-α	6 MU/day × 14 days → 6 MU/3 times/week × 22 week	6 Month	7	71.4% (5/7)	Clinical failure: two patients
Nomura et al. (2007)	Japan	Phase IV	Interferon-α	3 MU/day × 4–793 days (median 30 days)	6 Month	167	66.2% 29.2% (>1)	Side effects: 87.4% Serious side effects: 70%
Taylor et al. (2009)	UK and Japan	Double-blind RCT	Zidovudine + lamivudine	AZT 300 mg + 3TC 150 mg bd	48 Week	16	No clinical improvement	No change in proviral load
Macchi et al. (2011)	UK	Case series	Tenofovir	245 mg/day	2–16 Month	6	No clinical improvement	No change in proviral load

>1, improvement of more than one grade in the Osame's motor disability score.

No, number; qod, every other day; mo, month(s); yr, year(s); qd, every day; MU, million unit; wk, week(s); bd, twice daily; RCT, randomized controlled trial; AZT, zidovudine; 3TC, lamivudine.



Prognosis

To clarify clinical and laboratory findings that may be related to the pathomechanism of HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP), we analyzed these findings in 239 patients with HAM/TSP, including 64 patients followed up for 10 years after their first examinations, with special interest in the HTLV-I proviral load in peripheral blood mononuclear cells (PBMCs). The proviral load in PBMCs did not differ in terms of modes of HTLV-I transmission. However, the proviral load in patients with age of disease onset greater than 65 years tended to be higher than those with a younger age of onset. In the 64 patients followed up for 10 years, the clinical symptoms deteriorated in 36 patients (56%), unchanged in 26 patients (41%), and improved in 2 patients (3%). HTLV-I proviral load also appeared to be related to the deterioration of motor disability in these patients. To our knowledge, the present study is the first longitudinal study concerning the relationship between the clinical course of HAM/TSP and HTLV-I proviral load. It is suggested that HTLV-I proviral load is related to the progression of motor disability and is an important factor to predict prognosis of patients with HAM/TSP.

JAMA Network

From: Natural History of Human T-Lymphotropic Virus 1–Associated Myelopathy A 14-Year Follow-up Study

Arch Neurol. 2006;63(11):1560-1566. doi:10.1001/archneur.63.11.1560

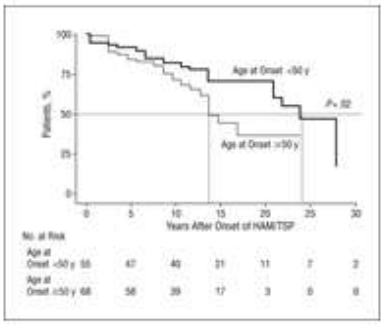


Figure Legend:

Kaplan-Meier estimates of the time from onset of human T-lymphotropic virus 1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) to assignment of a score of 8 on the Kurtzke Disability Status Scale (DSS) according to a younger vs an older age at onset.

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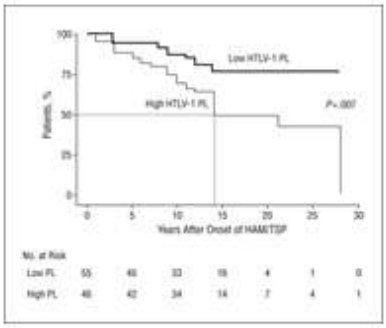


Figure Legend:

Kaplan-Meier estimates of the time from onset of human T-lymphotropic virus 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) to assignment of a score of 8 on the Kurtzke Disability Status Scale (DSS) according to a high vs a low HTLV-1 proviral load (PL) in peripheral blood mononuclear cells.

پلی نوروپاتی

- شایعترین تظاهر عصبی بعد از میلوپاتی گاهی بصورت خالص و گاهی همراه میلوپاتی(میلونوروپاتی) باشد.
- همانند سایر تظاهرات در خانمها شایعتر است بطور معمول در دهه سوم و چهارم دیده میشود.
- سیر بصورت تحت حاد یا مزمن می باشد.مواردی از سندرم گیلن باره گزارش شده است.
- حسی ,حرکتی, حسی حرکتی, اکسونال ,دمینیلیزان باشد.
- در یک مطالعه ۶۸درصد اختلالات NCVدراعصاب محیطی داشتند.۳۸/ مونونوروپاتی (عمداتا مدین) ۲۴/ مونونوروپاتی مولتیپلکس ۳۸/ پلی نوروپاتی (۸۴/۶ حسی-حرکتی ۱۵/۴ حرکتی خالص)

پلی نوروپاتی

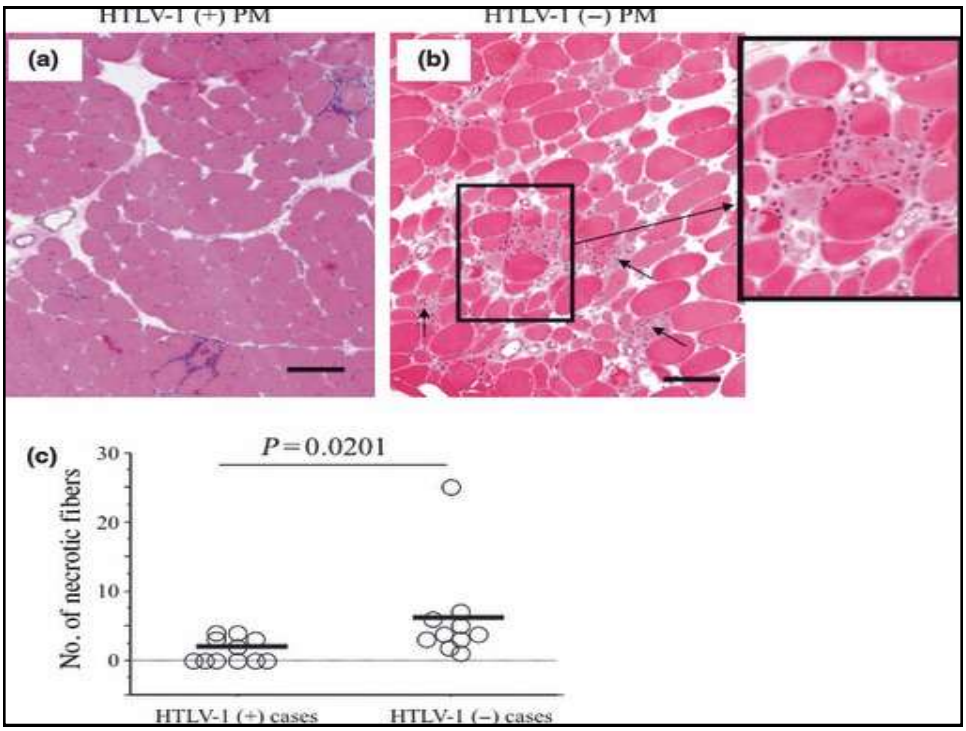
- تشخیص علایم بالینی و الکترودیکنوستیک
- تشخیص افتراقی در مورد میلونورویاتی محدود کمبود B12 ,سیرنگومیلی,اتاکسی فریدرایش, ALS,
- درمورد پلی نوروپاتی خالص مشکل است
- درمان قطعی ندارد. نگدارنده شامل فیزدوتراپی, پارستزی تری سیکلیک و گاباپنتین

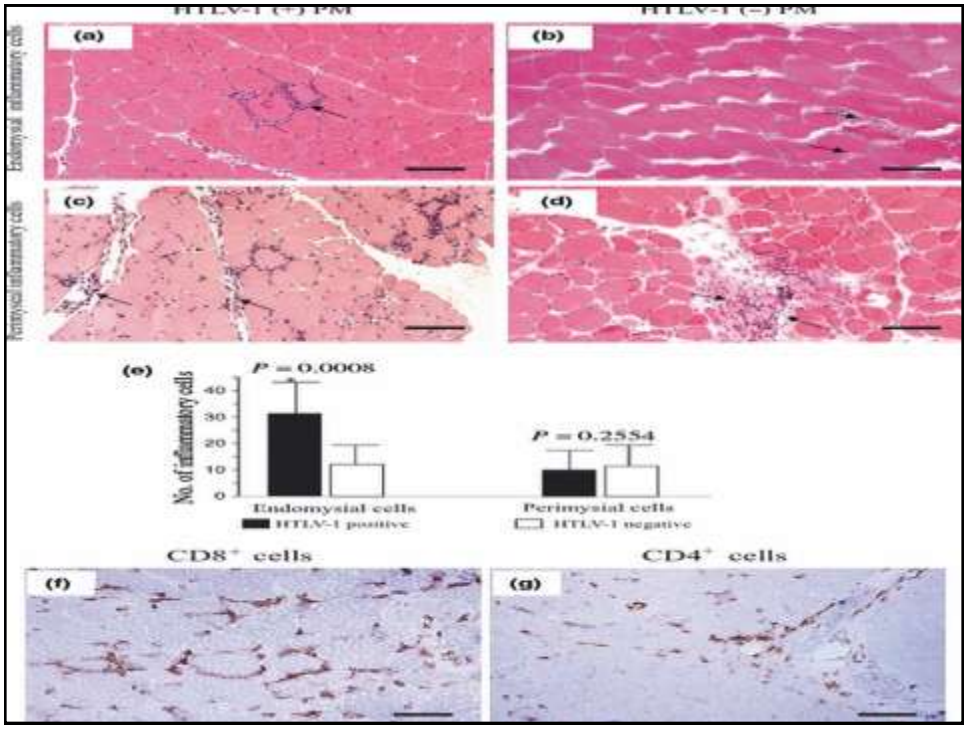
پلی میوزیت

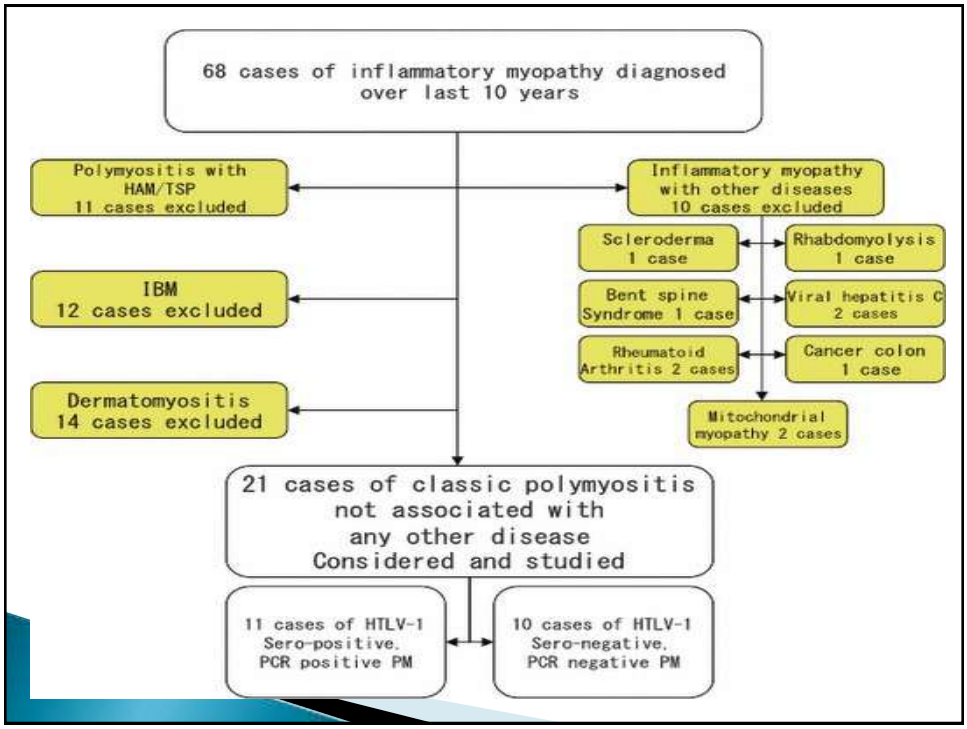
- در خانمها شایعتر است. از پلی میوزیت تیپیک سن شیوع بالاتر (۴۶سال به ۳۴)وسیر کند تر(ماه۳۲به ۱۳) دارد.
- بصورت تحت حاد یا مزمن ضعف پیشرونده کمربند لگنی و بعد کمربند شانه‌ای
- درد ناحیه کمر, درد عضلات , اختلال بلند شدن ,کاهش وزن,تب,سردرد,تورم اندام تحتانی,افتادن مکرر شکایت شایع بیماران است.
- اگر با میلوپاتی باشد علایم حسی حرکتی و اسفنکتری ناشی از ان دیده میشود.

پلی میوزیت

- EMG NCVپترن میوژنیک
- ازمایشات: CK LDH ,الدولاز فزایش می یابد ولی به اندازه پلی میوزیت ودرماتومیوزیت تیپیک نمی باشد.حتی کراتین کیناز می تواندطبیعی باشد.
- مانند پلی میدزیت تیپیک ESRبالا انتی بادی anti jo-1و ANA RFوبندرت anti -ro/ss-a anti la/ss-bدر خون محیطی مثبت است.
- آزمون سرولوژیکی anti htlv-1 و PCR مثبت است.
- پاتولوژی وپاتوژنز: با مکانیسم ایمنی ارتشاح سلول‌های تک هسته‌ای در عضلات دیده می‌شود.
- درمان: برخلاف پلی میوزیت تیپیک به کورتیکواسترویت پاسخ مناسبی نمی دهد. شاید بعلت سیر کند تر و تشخیص دیرتر که د ر درمان موثر است واز طرفی کورتیکواستویت با عوارض بیشتری نسبت به پلی میوزیت تیپیک همراه است.سایتوتوکسیکها به تنهایی یا با کورتیکو استرویید جواب مناسبی نداشته است.




HTLV-1 (+) PM
HTLV-1 (−) PM
(a)
(b)
(c)
(d)
(e)
P = 0.0008
P = 0.2554
No. of inflammatory cells
Endomysial cells
Perimysial cells
HTLV-1 positive
HTLV-1 negative
CD8+ cells
CD4+ cells
(f)
(g)


68 cases of inflammatory myopathy diagnosed over last 10 years
Polymyositis with HAM/TSP 11 cases excluded
Inflammatory myopathy with other diseases 10 cases excluded
Scleroderma 1 case
Rhabdomyolysis 1 case
IBM 12 cases excluded
Bent spine Syndrome 1 case
Viral hepatitis C 2 cases
Rheumatoid Arthritis 2 cases
Cancer colon 1 case
Dermatomyositis 14 cases excluded
Mitochondrial myopathy 2 cases
21 cases of classic polymyositis not associated with any other disease Considered and studied
11 cases of HTLV-1 Sero-positive, PCR positive PM
10 cases of HTLV-1 Sero-negative, PCR negative PM

In order to find out patients with early stage of HAM/TSP, we started HTLV-1 carrier clinic in the endemic area, Kagoshima, Japan, in 1999.
Till the end of 2012, 407 persons have visited the clinic as first time-visitors of HTLV-1 carriers, and 6 cases were diagnosed as early stage of HAM/TSP. These 6 cases are 1 male and 5 females, 20-55 years old (mean=41.8) at the diagnosis, no history of blood transfusion, and 4 cases have family history of HAM/TSP.
They could run and had no subjective symptoms on motor function, but all had subjective symptoms either dysesthesia/pain or urinary disturbances.
Physical examination demonstrated hyper-reflexes of lower extremities with mild spasticity, positive Babinski signs, and decreased sweating of lower trunk and legs.

Laboratory test showed positive anti-HTLV-1 antibodies in both sera and CSF, and proviral loads in the blood were high (386-2181 copies/104 PBMC) in all cases.
Two cases were treated with steroids and their urinary disturbances were improved. After 2 years of follow up, their symptoms remained unchanged and decrease of proviral load was obtained in one case.
These experiences indicate that early diagnosis of HAM/TSP is possible by careful medical checking of HTLV-1-positive individuals.
Decrease of sweating in lower body, and hyper-reflexes of legs with typical Babinski sign are important signs for early diagnosis.
Treatment intervention at early stage of the disease might improve functional prognosis of HAM/TSP patients.

In the present 25-year-study time, we report a significant decrease of HAM/TSP incidence estimated more than 70% in early 2000 compared to 1986-2000 period in Martinique a French West Indies Island.

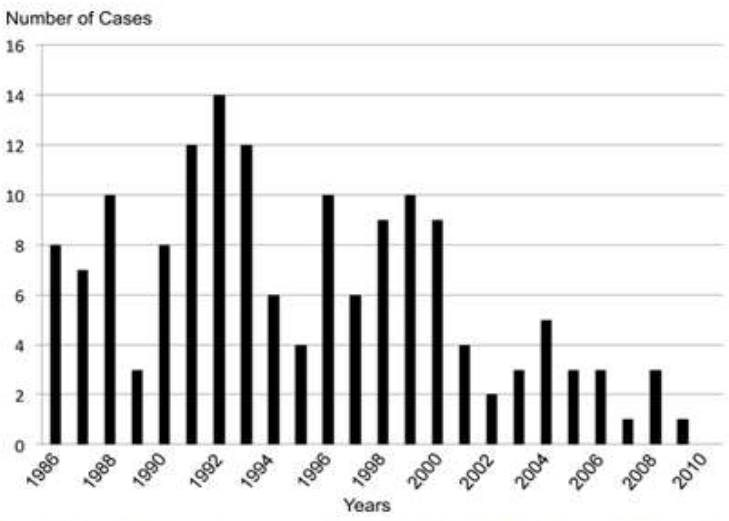
We found a trend to a significant older age at onset after 2000 (52.1 years versus 57.5 years, p = 0.06) that may reflect an age cohort effect and that could be indicative of a rapid decrease in HTLV-1 seroprevalence.

We showed a significant decline in HTLV-1 infection among first-time blood donors between 1996-2000 and 2011-2015 study periods.

Thus, probable HTLV-1 seroprevalence decrease secondary to HTLV-1 antibodies screening in blood donors and pregnant women and to iterative information campaigns could partly account for HAM/TSP incidence decline.

This study emphasizes the importance of prevention strategies to control HAM/TSP development in HTLV-1 endemic areas.

Fig 1. Number of HAM/TSP diagnosis per year over the 25-year study period.



Olindo S, Jeannin S, Saint-Vil M, Signate A, Edimonana-Kaptue M, et al. (2018) Temporal trends in Human T-Lymphotropic virus 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis (HAM/TSP) incidence in Martinique over 25 years (1986-2010). PLOS Neglected Tropical Diseases 12(3): e0006304. https://doi.org/10.1371/journal.pntd.0006304
http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006304&rev=1

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