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Teaching Course 13

Nervous system disorders due to retroviruses (Level3)

Neurological disorders due to HTLV - an emerging issue in migrants to Europe

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Conflict of Interest

In relation to this presentation and manuscript:

❑ the Author has no conflict of interest in relation to this manuscript.

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Neurological disorders due to HTLV-1 – an emerging issue in migrants to Europe

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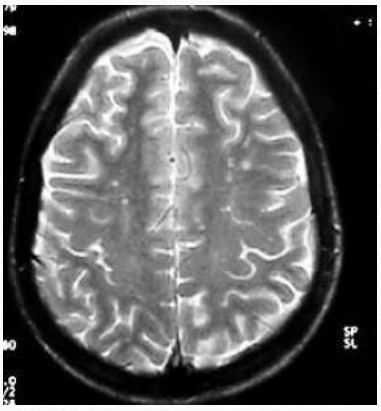
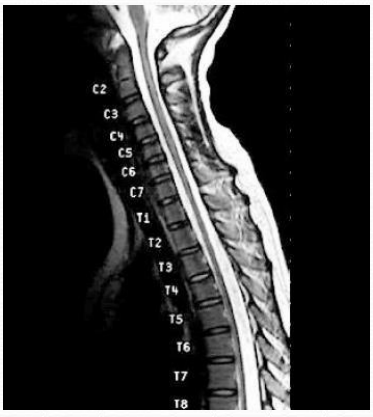
A young female with limb weakness

- 19 year old Brazilian female
- 4 year onset of walking difficulties, clumsiness and urine urgency
- Recurrent urine infections
- Exam:
  - brisk reflexes
  - pareto-spastic gait
  - Babinski sign
  - lower limb weakness 4/5 in quadriceps and iliopsoas
- HIV (-), syphilis (-)
- CTD (-)
- B12 / folic acid normal
- Copper level normal
- MRI: high T2 signal areas in spine and brain white matter
- Urodynamic study: overactive bladder

MRI of brain and whole spine





Carod Artal, Rev Neurol, 1999

Diagnosis: TSP/HAM

- CSF:
  - 22 lymphocytes,
  - increased IgG index
  - Non-exclusive OCBs
- Serum:
  - ELISA: HTLV-1 +
  - Western blot on serum and CSF: HTLV-1 +

The discovery of HTLV-1 virus

- 1980, Poiesz:
  - First retrovirus isolated from lymphocytes in a cutaneous adult T-cell lymphoma (ATL)
- Viral genome from HAM cell lines similar to ATL cell lines
- Martinique, Vernant, 1987:
  - 78% serum positive antibodies to HTLV-1 among 25 TSP patients
- Japan, Osame, 1986:
  - multilobulated "flower" lymphocytes in blood/CSF
  - positive HTLV-1 Abs
  - HAM: HTLV-1 associated myelopathy

The virus, HTLV-1

- Retroviridae family, Deltaretrovirus
- Positive single-stranded RNA virus
- Provirus: double-stranded inserted form within the host cell DNA
- Replication strategy: to convert the single RNA strand into a double-stranded DNA in order to insert it into the host cell DNA

- HTLV-1, HTLV-2
- HTLV- 3 and 4: bushmen in Central Africa

- Genetic stability

- 4 geographic subtypes (genotypes)
  - Cosmopolitan subtype: A
  - Central African: B
  - Australo-Melanesian: C
  - Central Africa/pigmies: D

- Rare subtypes: E,F,G in Central Africa

Epidemiology, endemic regions

- Japan
- Central America: Jamaica, Caribbean
- South America: Peru, Colombia, Brazil, Venezuela, Bolivia
- Africa: Uganda, Tanzania, Zaire, Gabon, Ivory Coast
- Melanesia, New Guinea, Australia
- Middle East: Iran

- Seropositivy rate:
  - 1%, Central Africa
  - 3-6% , Trinidad, Jamaica, Caribbean
  - 10% South-East Japan
    - 37% Kyushu island
    - 30% Miyazaki rural areas

- Seroprevalence increases with age; double rate in female:
  - Jamaica: >70 years:
    - 9.1% males
    - 17.4 % females
  - Hokaido, Japon: >80 years:
    - 50% females
    - 30% males

HTLV-1 infection in non-endemic areas

- Worldwide: 10-20 million people infected
- Prevalence in US blood donors: 0.025%
- First-time blood donors in Europe: <0.4/10,000
- Romania: endemic area: 5.3/10,000 blood donors
- Seroprevalence Europe among pregnant: 0.01-0.1%

- Groups at risk
  - Sex workers
  - Intravenous drug abusers: Spain, Italy, Ireland
  - Immigrants from endemic areas along with their sexual partners and children
  - Transplant recipients and blood donors

Gessain, and Cassar; Frontiers Neurol, 2012

HTLV-1 infected people in Europe

- 80% are immigrants or descendants from endemic areas (West Indies, Africa, Latin America)
- HTLV carriers:
  - UK: Jamaica, Barbados, Ghana
  - France: West Africa, Martinique/Guadaloupe
  - Spain: South America
  - Portugal: Africa

- Estimations:
  - UK: 20,000-30,000 people
  - Cosmopolitan France: 10,000-25,000
  - Romania: 3,000-15,000
  - Spain: 1,000-8,000
- HTLV-1 clusters in specific country or populations

Gessain, and Cassar; Frontiers Neurol, 2012

Implications for Public health in Europe

- Spain:
  - Nation-wide register: 351 HTLV-1 infected people
  - only 23% of new HTLV-1 diagnosis were symptomatic
  - Women 62%; native 12%
- Underdiagnosis must be common
- Screening in blood bank needed
- Screening on transplant donors needed
- Within European union, most HTLv-1 infections are detected in people with black ethnicity, coming from Caribbean and sub-Saharan region, and from Latin America
- Misdiagnosis of asymptomatic carriers leads to late diagnosis
- HIV/HTLV-1 co-infection, 1.6%

De Mendoza, OFID, 2019

HTLV-1 infection: transmission mechanisms

1. Sexual transmission

- Transmission rate 15%
- 4 times more effective from male to female
- Increased seroprevalence with age in women
- Transmission risk:
  - 4.9 / 100 people/year among female partner of infected male
  - 1.2 / 100 among male partner of infected female
  - Increased if pennis ulcer and syphilis are present

2. Transfusion/blood products

- Less efficient than in HIV
- Blood products containing HTLV-1 infected lymphocytes associated with high rate of infection: 40-60%
- At least 90,000 HTLV-1 infected cells are needed to promote infection in the recipient
- Average time to seroconversion after transfusion: 50 days
- Intravenous drug users
- Solid organ transplantion: high risk of rapid clinical progression

3. Transmission from infected mother to child

- Breastfeeding: prospective studies in Japan and Jamaica
- Risk factors:
  - Prolonged breastfeeding after 6 months of age
  - High HTLV-1 proviral load in milk and blood cells
  - High HTLV-1 antibody titers in the serum
- Transmission rate: 10-25%

HTLV-1 diseases:

Adult T-cell leukemia/lymphoma (ATLL)

Tropical spastic paraparesis / HTLV-1 associated myelopathy (TSP/HAM)

Ophthalmic: Uveitis, optic neuritis
Polymyositis and inclusion body myositis
Lung:
- chronic lymphocytic alveolitis
- bronchiectasis among Australian aborigens

Joints: chronic back pain, joint pain, arthropathy
Sjögren syndrome / thyroid disease

Other infectious diseases and oportunistic infections:
- *Strongyloides stercoralis* *
- crusted scabies / leprosy / TBC
- urine infections / interstitial cystitis / chronic prostatitis
- children: chronic infective dermatitis (*S. aureus* / beta-hemolytic *Streptococcus*)
- HIV/HTLV-1 co-infection

* Decreased IgE secretion in HTLV-1 infected patients

Neurological manifestations HTLV-1

HTLV-1 associated myelopathy: TSP/HAM
- classical form
- rapidly progressive myelopathy
- cerebellar sydrome with ataxic gait
- MND/ALS pattern

Subcortical cognitive decline
Axonal/mixed peripheral polyneuropathy
Polymyositis
Facial palsy
Involvement of other cranial nerves

Risk of developing TSP/HAM

- Epidemiological studies among carriers
  - Lifetime risk of developing ATLL: 2-6%
  - 1-4% risk of developing HAM/TSP
- Incidence HAM/TSP in endemic area: 2 cases/100.000 inhabitants/year
- Around 5% may develop any HTLV-1 disease (?)
- Recent studies suggest a life-time risk 10-fold higher*
- Symptoms onset: age 30
- Adult females
- Sporadic but family clusters may occur
- Dermatitis common in TSP/HAM teenagers
- Heterogeneous progression
  - Insidious course
  - Rapidly progression

* Tanajura et al, Clin Infect Dis 2015

Risk factors associated with TSP/HAM

- Higher levels of proviral load
  - TSP/HAM patients have proviral load in CD4+ cells up to 10 times higher than carriers
- HLA class I alleles
  - HLA-A*02 and HLA-C*08: lower proviral load and lower risk of TSP/HAM
  - HLA-B54* allele: significant increase risk for TSP/HAM and proviral load
- Via of transmission: breasfeeding?
- Level of immune response: CTLs response to TAX gen proteins
- HTLV-I subtype (A: Cosmopolitan; B: Africa; C: Melanesia)

Pathogenesis

A) CD4+ T-cells infected by HTLV-1 migrate to CNS

- CD8+ cytotoxic T cells lyse and kill infected Tax-expressing CD4+ target cells , HBZ and other viral antigens
- TSP/HAM patients have high levels of CD8+ virus-specific CTLs in blood and CSF
- High rate of lysis is linked wit lower proviral load

B) Proliferation and clonal expansion of autoproliferative infected CD4+ cells
Cross-reaction though molecular mimicry with host CNS antigens

C) Bystander damage:
IFN-y-secreting HTLV-1 infected CD4+ T cells are recognised by CD8+ CTLs and induce microglia to secrete toxic cytokines and TNF-alpha

Complex proteins and pathogeneses

Tax protein

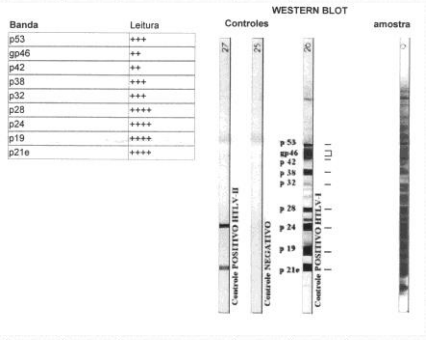
- Product of the transcriptional regulatory gene Tax
- Acts as an oncogenic protein (T cell-leukemia)
- Involved in the pathogenesis of TSP/MAH
- Autoimmunity?
  - Polyclonal antibodies show cross reactivity between Tax epitope and nuclear ribonucleoprotein A1
- Tax-A present in 84% TSP/MAH vs 28% in asymptomatic carriers
- Furukawa, 2000: 2.5 highest risk of suffering from TSP/MAH if:
  - raised proviral DNA and
  - absence of HLA * 02 and
  - presence of Tax-A

HBZ transcription factor

- HBZ: complex gene
- Regulatory RNA which promotes proliferation of host cells
- HBZ protein: activates TGF-beta pathway
- Inflammatory response in HTLv-1 infection may be caused by HBZ
- HBZ: dominant factor in leukemic transformation

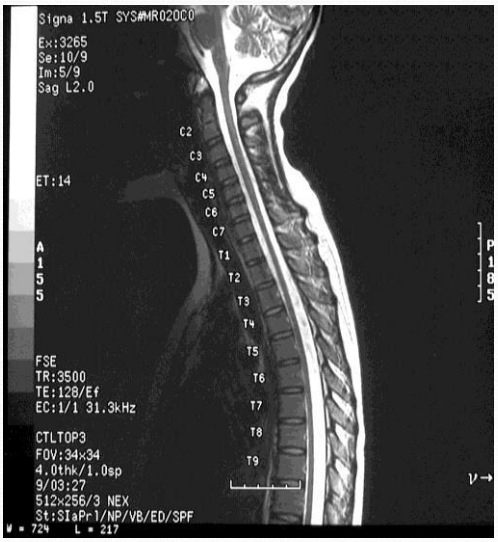
Tagaya et al, F1000Research, 2019

Diagnosis



- Serum
  - OCBs
  - Flower lymphocytes
  - Serological assays
    - Screening: ELISA
    - Confirmatory test: IFA, western-blot
  - PCR: analysis of integrated provirus in DNA from peripheral blood cells
  - PBMC proviral load
- CSF:
  - Mononuclear pleocytosis
  - Flower lymphocytes
  - Normal glucose level
  - Raised protein level
  - OCBs
  - Increased IgG synthesis index
  - Positive anti-HTLV-1 Abs (ELISA/WB
  - CSF cell proviral load increased
  - Tax antigen in CSF

HTLV-1 associated myelopathy



- Progressive, slow course
- Onset: 30-40 (range: 20-70 years)
- Lower limb weakness
- Spasticity
- Brisky reflexes, clonus, Babinski sign
- Sensory symptoms/paresthesias
- Neurogenic bladder dysfunction
- Impotence
- Back pain

A series of cases

- 42 of 249 paraparetic patients (16.9%)
- 26 females
- Mean age: 49.8 years
- Mean time from symptom onset to dignosis 11.2 years (range: 1-40 years)

- Half of patients were wheel-chair restricted or had a domiciliary walk
- Mean EDSS 6. Barthel mean score 65
- Syndromes:
  - Hyperreflexia, ankle clonus and bilateral Babinski sign: 97.7 %
  - Lower limb proximal muscle atrophy: 28.6 %
  - Gait ataxia: 21.4%
  - Peripheral neuropathy: 7.1%

- CSF findings:
  - Increased IgG intratecal index
- MRI findings:
  - Thoracic spinal cord atrophy: 66.7%
  - White matter hyper-intensity areas in subcortical white matter (42.8 %) and spinal cord (21.4%)
  - Thoracic cord high signal areas: 14%

Carod Artal, Neurologia 2008

Neurological manifestations

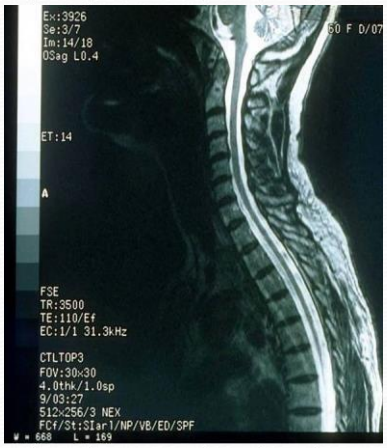
	n	%
Paraparesis	42	100
Hiperreflexia /brisky reflexes	41	97.7
Babinski sign	40	95.2
Distal hipopalesthesia	33	78.6
Lower limb paresthesias	21	50
Neuropathic pain	16	38
Decreased visual accuracy	16	38.1
Lower limb proximal muscle wasting	12	28.6
Dysmetria	9	21.4
Fasciculations	8	19.5
Upper limb muscle wasting	5	11.9
Optic nerve atrophy	2	4.8

Carod Artal, Neurologia 2008

TSP/HAM: systemic manifestations

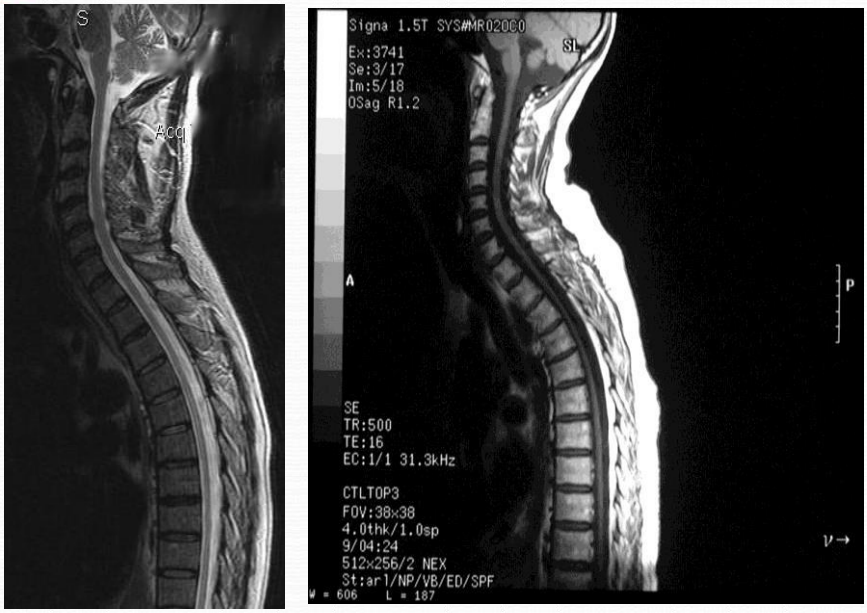
	n	%
• Urine incontinence	28	66.7
• Back pain	24	57.1
• Chonic dermatitis /dry skin	23	54.8
• Recurrent urine infections	23	54.8
• Sjogren syndrome, dry eye/mouth	19	45.2
• Urine urgency	14	33.3
• Joint pain	13	30.9
• Sexual dysfunction	12	28.6

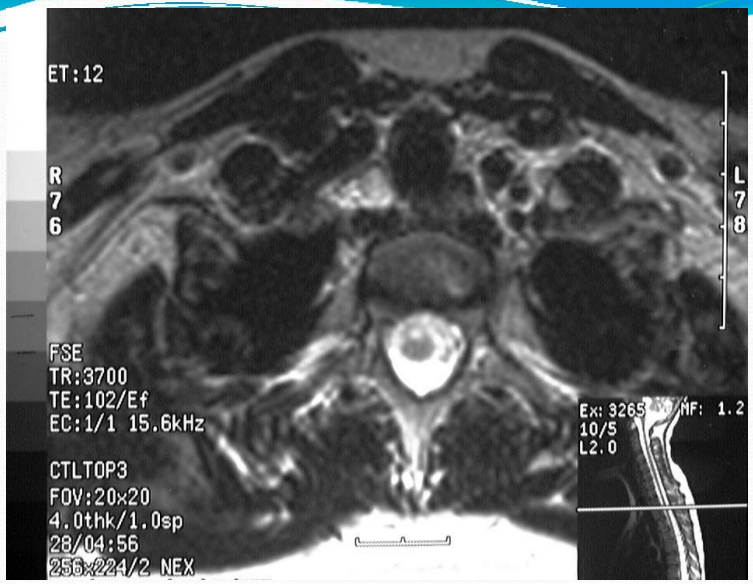
Spinal cord and brain MRI findings

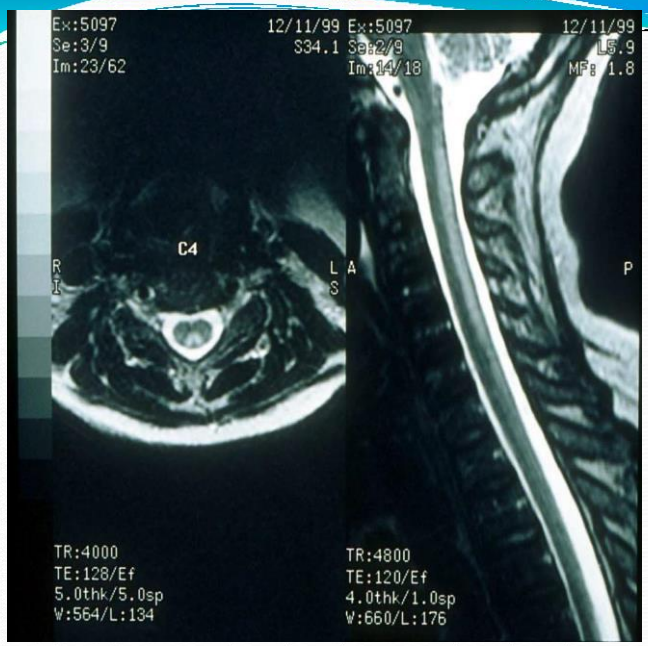


- Subacute myelitis
- Thoracic spinal cord
- High signal T2 lesions
- Gadolinium enhancement in subacute cases
- Spine atrophy in late cases
- Brain: white matter abnormalities

Spinal cord atrophy in late stages

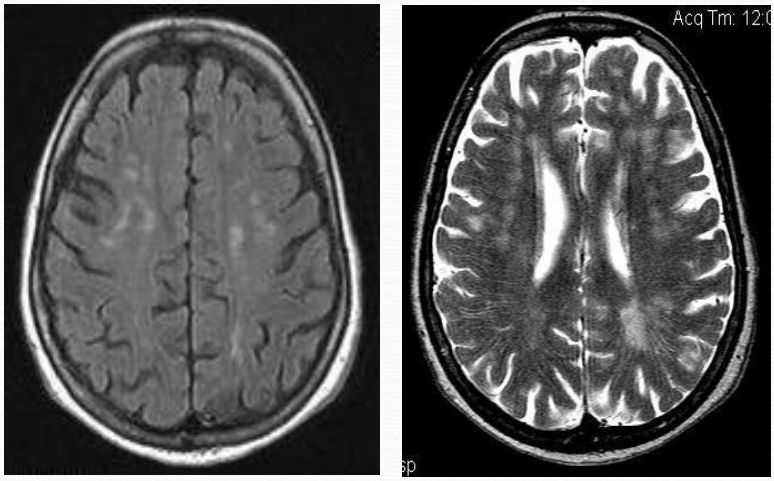






Subacute myelitis caused by HTLV-1 infection

White matter abnormalities on brain MRI



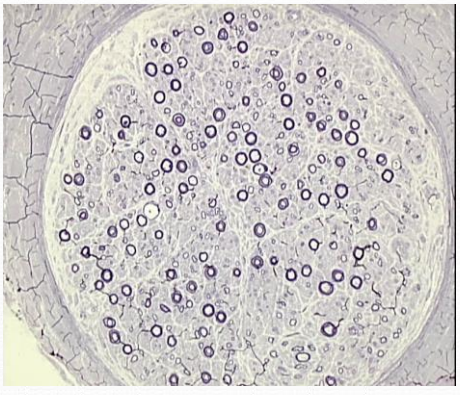
HTLV-1 inflammatory myopathy

- Jamaica: Mora (1988), Morgan (1989); polymyositis in absence of TSP/HAM
- Japan: Higuchi (1992); high rate of HTLV-1 in polymyositis
- Japan: Inose, biopsy-proven polymyositis:
  - 35% + HTLV-1 (11/35) compared to 12% seroprevalence rate in general population
- Pathological findings:
  - Mononuclear cell infiltrates
  - Necrosis, atrophy and fibrosis
  - Internalization of nuclei
  - No evidence of myocyte infection
- Tax mRNA-positive $CD4$ cells
- Proximal 4-limb weakness
- Bilateral lower limb weakness
- Muscle pain and muscle wasting
- With or without TSP/HAM
- EMG: myopathic findings
- Denervation in concurrent TSP/HAM
- CK levels:
  - Raised in Jamaican patients
  - Inose cases, only 2/6 raised
- No direct pathogenic role of HTVL-1 on muscle fibers

Amyotrophic lateral sclerosis-like disease and HTLV-1 infection

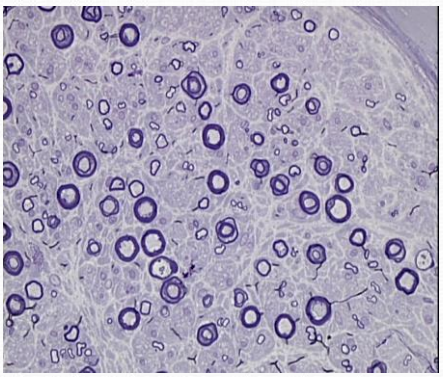
- Rare condition
- Cases reported in Brazil
- Progressive course, around 10 years
- Muscle weakness and atrophy
- Bladder dysfunction and sensory symptoms
- Necropsy studies:
  - Gliosis of hypoglossal nucleus
  - Anterior horn cell loss

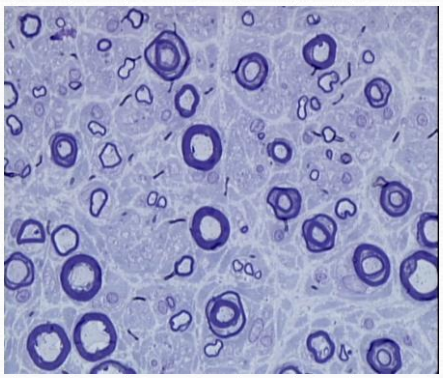
HTLV-1 polineuropathy



- 5% TSP/MAH patients
- Paresthesias, burning sensation and distal hypoesthesia
- NCS: decreased amplitudes and slow velocity
- Sensory/motor neuropathy
- Pure sensory neuropathy in absence of TSP/HAM
- Autonomic PNP
  - Orthostatic hypotension
  - Sweat dysfunction

Axonal sensory-motor HTLV-1 polineuropathy





Ophtalmic involvement

Uveitis / retinal vasculitis

- In HAM/TSP
- In HTLV-1 carriers with no myelopathy

- Visual gaze or floaters
- Granulomatous reaction
- Vitreous opacities

- It may respond to steroids

Keratoconjunctivitis sicca

- Found in one third of Jamaican seropositive patients

- Interstitial keratitis, 10%

TSP/HAM: disability progression

Rapid progression

- Severe gait impairment at 1-3 months
- On wheel-chair at 2 year onset

- Risk factors:
  - Transmission via Transplantation
  - Blood transfusion
  - Mean age> 50 at symptom onset
  - High proviral load> 10^5 DNA copies/ 10^6 PBMCs
  - High antibody titers

Classical TSP/HAM

- 17% progression at 4 years
- Cane of walking: 6 years
- EDSS 6: 6-11 years
- Walker device: 13 years
- Wheel-chair: 21 years

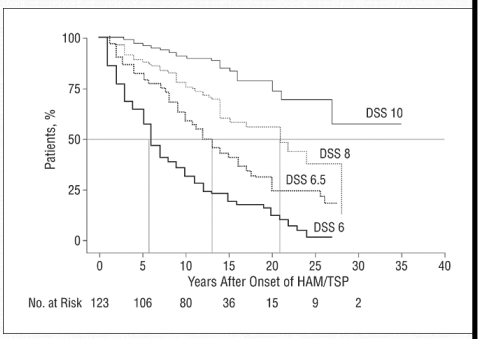
- PPMS: EDSS 6 at 6-8 years

Olindo et al,2006; Carod Artal et al, 2008

Risk having EDSS 8 at 14 year follow up

Variable	HR(CI 95%)	p
Age at onset > 50 years	3.0 (1,2-7,1)	0.01
Proviral load >10^6	2.7 (1,2-5,9)	0.02

n=123



Olindo et al, Arch Neurol 2006

Other prognostic factors

Mortality HTLV-I

Linked to TSP/HAM

- Neumonia and other respiratory infections
- Urinary sepsis, pielonephritis
- Skin lesions / infections
- Denutrition , caquexia
- Respiratory insuficiency and fibrose
- HIV co-infection

- Other causes
  - Cancer
  - Stroke

Co-infections

- HIV and HTLV-1 myelopathy
- Casseb, J Med Virol 2008: 38/296: 12.8%
- Carod-Artal, Neurología 2008: 1/43: 2.4%
- Co-infected patients have higher proviral load

- Hepatitis B – C
- Neuro-syphilis

Treatment

TSP/HAM

- Limitation: Few randomized placebo-controlled clinical trials

- Antiviral therapy
  - HTLV-1 reverse transcriptase inhibitors: zidovudine

- Inmmunomodulation therapies
  - Oral prednisolone
  - IV methyl-prednisolone
  - IFN-alpha, INF-beta
  - Pentoxifylline
  - Danazol
  - Teriflunamide
  - Histone deacetylase inhibitors: valproic acid
  - Plasmapharesis
  - IV Igs
  - Anti-IL-2R monoclonal antibodies
- Symptomatic treatment
  - Baclofen
  - Gabapentin

ATTL

- Chemotherapy

- Zidovudine and IFN-α

- Mogamulizumab
  - Humanized anti- CCRS chemokine receptor monoclonal antibody
  - Strong Ab-dependent cellular cytotoxicity

- Combination therapy: mogamulizumab + LSG15-based chemotherapy

Futsch, Viruses 2018

Interpheron studies in TSP/HAM

IFN- alfa

- Short-term benefit in 1 randomized study (n=48)
- Different treatment modalities
  - Izumu, 1996: 3 MU/day 30 days
  - Saito, 2004: 3 MU/day 14-21days + 3 times / week
- Decrease in proviral load, CD8 + CD45RA-CD27 + T cells

- Studies with small casuistry
- Patients with different degrees of disability and time of evolution

Saito et al, 2004; Izumo et al, 1996

INF beta

- Reduces the m-RNA load of Tax, which causes a reduction in the synthesis of viral proteins
- Reduces the frequency of specific CD8 + T cells
- Reduction of spontaneous lymphoproliferation in vitro
- Unaltered proviral load
- No significant clinical progression was observed
- Safe and well tolerated
- n = 12; 60 ug im 2 x week

Unsong et al, Ann Neurol, 2005

Prevention

A search for a vaccine

- Neutralizing antibodies
- HTLV-1 envelope gen induce partial protection against infection in rodents
- HBZ may act as protective CTL antigen: tested in mouse model
- Clinial trials needed
- An anti-HTLV-1 lentivirus vector-based vaccine
  - Encodes a polypeptide derived from Tax, HBZ, p12 and p30 HTLV-1 proteins
  - Safe
  - Induced cellular response in mice model

Preventative strategies

- Blood donor screening:
  - Japan, USA, France, Netherlands, Sweden, Portugal, Denmark, Greece, Ireland, Romania, UK
- Transplant donor testing: France, UK
- Sexual prevention: protected intercourse
- Routine antenatal screening and formula feeding of babies of HTLV-1 + mothers, Nagasaki 1987
- *Strongyloides stercoralis* screening among carriers
- Preventative therapy of asymptomatic carriers (valproate + antiviral drugs)?
- Screening among at-risk groups
- Education:
  - "HTLV Aware" UK
  - HAM-net (Japan)
  - Global Network's HTLV-1 Task-Force

Conclusions

- Progressive lower limb weakness, spasticiy and neurogenic bladder are TSP/HAM hallmarks
- Lower extremity weakness and back pain are common initial complaints
- Urine urgency and incontinence may precede gait/walking symptoms
- Cerebellar symptoms, cranial nerves and neuropathy are other features
- Think in TSP/HAM in patients migrating from endemic areas and groups at risk