Webinário

Vírus linfotrópico de células T humanas (HTLV): a ameaça silenciosa e suas manifestações neurológicas

30 Nov, 2023, 13:00 GMT/10:00 BR/AR

Registre-se

Tradução simultânea
PT-ESP-ING
Panel

**Chair:** Augusto César Penalva de Oliveira - Supervising Physician, Neurology Medical Team, Emílio Ribas Infectious Diseases Institute, Brazil

**Steven Jacobson** - Senior Investigator, Viral Immunology Section, Neuroimmunology and Neurovirology Division (NND), National Institutes of Health (NIH), USA

**Lucia Brito** - Neurophysiologist, Reference Center for the Care of Patients with Demyelinating Diseases, Restauração Hospital, Ministry of Health, Brazil

**Carlos Pardo** - Director, Johns Hopkins Myelitis & Myelopathy Center, Baltimore, Maryland, USA

**Clarice Neuenschwander** - Senior Researcher at the Laboratory of Virology and Experimental Therapy, Fiocruz Pernambuco, Fiocruz, Brazil.

**Cristiane Campello Bresani** – Senior Researcher at the Laboratory of Virology and Experimental Therapy, Fiocruz Pernambuco, Fiocruz, Brazil.
Resources

- https://portal.fiocruz.br/en
- https://fiocruz.tghn.org/
- https://lac.tghn.org/
- https://www.instagram.com/HTLVBrasil/
- https://fiocruz.tghn.org/health-topics/neuroinfeccoes/grupo-neuroinfeccoes/
HTLV and the human host: a long-standing interaction

Dr Steven Jacobson, PhD

Viral Immunology Section, Neuroimmunology and Neurovirology Division, National Institutes of Health, USA
Immunopathogenesis of HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP)
Human T-cell lymphotropic virus type 1 (HTLV-1)
Research of rare diseases can inform understanding of common neurological disorders
### HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis: Similarities and Differences with Multiple Sclerosis

<table>
<thead>
<tr>
<th></th>
<th>HAM/TSP</th>
<th>MS</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Chronic progressive myelopathy</td>
<td>Resembles primary progressive &quot;spinal&quot; form of MS.</td>
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<tr>
<td><strong>Oligoclonal Bands</strong></td>
<td>Yes To HTLV-I antigens.</td>
<td>Yes To unknown antigens.</td>
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<tr>
<td><strong>MRI</strong></td>
<td>Atrophy of spinal cord. Mimics CNS demyelination in brain similar to MS.</td>
<td>Demyelinating lesions of CNS white matter.</td>
</tr>
<tr>
<td><strong>Disease for life</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Etiologic Agent</strong></td>
<td>HTLV-I</td>
<td>Unknown: Viruses considered.</td>
</tr>
<tr>
<td><strong>Demyelination</strong></td>
<td>Yes Predominantly of corticospinal tracts, mild in posterior columns.</td>
<td>Yes Diffuse involvement of spinal cord white matter; Corticospinal and posterior columns severely affected</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Yes Present at all levels of CNS; Predominates in spinal cord at levels of severe demyelination.</td>
<td>Yes Moderate in CNS lesions.</td>
</tr>
<tr>
<td><strong>Lymphocytes In lesions</strong></td>
<td>Yes CD4 and CD8 early in disease; CD8 persist in late disease.</td>
<td>Yes Combination of CD4 and CD8.</td>
</tr>
<tr>
<td><strong>Immune Response</strong></td>
<td>Yes Spontaneous lymphoproliferation; High HTLV-I specific antibody and CTL.</td>
<td>Yes Activated T cells in CSF and blood.</td>
</tr>
<tr>
<td><strong>HLA association</strong></td>
<td>Yes Japanese associated alleles</td>
<td>Yes HLA DRB1*1501</td>
</tr>
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</table>
Outcomes of HTLV-1 infection

- Asymptomatic carrier (90-95%)
- Adult T cell leukemia/lymphoma (2-5%)
- HTLV-1 associated myelopathy/tropical spastic paraparesis (0.25-3.8%)
- Other inflammatory manifestations: Arthropathy, uveitis, dermatitis, polymyositis, pneumonitis, other (?)

HTLV-1 infected people: 10-20 million

Seroprevalence of HTLV-I/II

Viral Immunology Section- HTLV-I/II Clinic
Protocol Participants: Country of Origin

HTLV1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP)

- Myelopathy – disease related to the spinal cord
- Demographics: females>males, median age 45-55 years
- Symptoms:
  - Back pain
  - Lower extremity weakness, falls
  - Stiffness
  - Urinary incontinence
  - Bowel incontinence or constipation
  - Sexual dysfunction
  - Sensory disturbances

Clinically suggests disease process is in thoracic cord

http://hamtsp-net.com/english/about/index.html
425 patients
(HAM/TSP, Asymptomatic carriers (AC), HTLV-2 patients, HTLV-I/II seroindeterminates, family members)

Biobanked samples
31710 PBMCs
5585 serum
922 CSF
102 saliva
250 plasma
Association of Viruses and Chronic Progressive Neurologic Disease

**Translational Studies**

**HTLV-I** → **known etiology** → **HAM/TSP**

**Virus?** → **suspected etiology** → **Multiple Sclerosis**

- **Anti-tac**
- **Daclizumab**
- **β-interferon**
- **Teriflunomide (Aubagio)**

**Treatment**
HTLV-I

How Can Virus That Affects Millions of People Be Associated With Disease in a Small Subset of Patients?

- Virus
- Genetics
- Host Immune Response
Etiology of Multiple Sclerosis

Environmental factors
- Geographic distribution
- Migration studies
- Outbreaks

Immunological factors
- Pathology
- CSF Ig Abnormalities
- T cell Abnormalities
- Relationship to EAE

Genetic factors
- Increased risk in families
- Increased risk in monozygotic twins
- Association with genetic markers
- Low risk in some ethnic groups
Number of subjects

D ~0.5 ~1 ~1.5 ~2 ~2.5 ~3.5

Asymptomatic Carriers

HAM/TSP Patients and Carriers

Distribution pattern of HTLV-I Proviral Load in PBMC of HAM/TSP Patients and Carriers

Log10 (HTLV-I proviral load / 10^4 PBMC)
HAM/TSP is Characterized by an Activated Immune Response

- HTLV infection
- Viral mRNA and protein expression
- Inflammatory cytokine expression

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Asymptomatic carriers</th>
<th>HAM/TSP</th>
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</thead>
<tbody>
<tr>
<td>Proviral DNA load</td>
<td>Lo</td>
<td>Hig</td>
</tr>
<tr>
<td>Viral mRNA load</td>
<td>w</td>
<td>h</td>
</tr>
<tr>
<td>Virus-specific CD8(^+) T cell</td>
<td>Lo</td>
<td>Hig</td>
</tr>
<tr>
<td>Spontaneous proliferation</td>
<td>w</td>
<td>h</td>
</tr>
<tr>
<td>Inflammatory cytokine production (IFN-(\gamma), TNF-(\alpha))</td>
<td>Lo</td>
<td>Hig</td>
</tr>
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</table>
Induction of HTLV-I specific T cell Responses

DNA PCR  RNA PCR  TCR-like antibodies  HLA A201/tax tetramers

HTLV-I tax specific CD8+ T Cells
Tax mRNA expression Protein (peptide loaded HLA)

DNA  RNA  peptide  T cells

CD4+ HTLV-I

Induction of HTLV-I specific T cell Responses

Yamano et al., Blood 99:88, 2002

TCR-like antibodies

Yamano et al., Blood 99:88, 2002


Oh, et al., Blood, 117: 3363-3369, 2011,


Enose-Akahata et al., Plos Pathogen 5(12):2009

Yamano, et al., Plos One 4(8), 2009,

Grant et al., Blood 15:5601-5609, 2008
CD8+

T cell Recognition of MHC/peptide Complexes

HLA A201/tax tetramers
Research of rare diseases can inform understanding of basic immunology
Class I MHC (HLA-A2)

HTLV-I Tax peptide:
L L F G Y P V Y V

HTLV-I-specific CD8+ TCR

Lessons from HAM/TSP

HTLV-I Tax-specific CD8+ T cells increased in HLA A201 PBMC from HAM/TSP patients (NIH and Japan)
Expansion of HTLV-I tax11-19 Tetramer Reactive CD8+ Cells in the CSF of HAM/TSP Patients

HAM/TSP patient

HAM/TSP patient

HAM/TSP patient

Tax-Tetramer  CMV-Tetramer

PBM C

CSF cells

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF

Tax-Tetramer  CMV-Tetramer

PBM C

CSF
HTLV-I proviral load is increased in CSF of HAM/TSP patients
digital droplet PCR (ddPCR)
Differentiation of HAM/TSP from patients with multiple sclerosis infected with HTLV-I

M. Puccioni-Sohler, MD, PhD; Y. Yamano, MD, PhD; M. Rios, PhD; S.M.F. Carvalho, PhD; C.C.F. Vasconcelos, MD; R. Papais-Alvarenga, MD, PhD; and S. Jacobson, PhD

**Table 2** Mean ± SD of PBMC and CSF of 17 HAM patients (Group I) in comparison with 18 non-HAM patients (Group II)

<table>
<thead>
<tr>
<th></th>
<th>HAM/TSP (Group I), n = 17</th>
<th>Non-HAM/TSP (Group II), n = 18</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC HTLV-I proviral load/100-cell copies</td>
<td>38 ± 26</td>
<td>9 ± 5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CSF HTLV-I proviral load/100-cell copies</td>
<td>83 ± 5</td>
<td>1.9 ± 5</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

PBMC = peripheral blood mononuclear cells; HAM/TSP = human T lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis.
Model of Immunopathogenesis in HAM/TSP

Peripheral blood
- CD4+ T cells
- CD8+ T cells

Monocyte/macrophage

Central Nervous System
- HTLV-I provirus
- HTLV-I antigen
- HTLV-I specific CD8+ cell
- Neurotoxic cytokines (IFN-γ, TNF-α)
- Damaged Neuron
- Glial cells

Responding and Proliferating cells
- Expansion

Immune response to HTLV-I antigen expressing cells

Blood Brain Barrier
Can HTLV-I Specific CD8+ T cells be detected in the CNS of HAM/TSP Patients?
Inflammatory CD8+ Cells in HAM/TSP Spinal Cord

H&E

CD3+

CD8+

CD4+
Detection of HTLV-I in GFAP+cells in HAM/TSP CNS Samples

HAM/TSP - biopsy

CD 3 - pan T cell marker

Grains = HTLV-I tax RNA

in situ - hybridization

HAM/TSP - autopsy

Case 1

Grains = HTLV-I tax RNA
Red = GFAP

in situ - hybridization

Case 2

Grains = HTLV-I tax DNA
Brown = GFAP

in situ - PCR
HTLV-I specific CTL in HAM/TSP Spinal cord autopsy:

HAM/TSP spinal cord parenchyma

HAM/TSP spinal cord meninges

HTLV-I
Tax11-19
tetramer (red)

Eiji Matsurra
Spinal Cord Atrophy in HAM/TSP and Correlation with CSF Immunophenotyping

Cervical and thoracic cord atrophy in multiple sclerosis phenotypes: Quantification and correlation with clinical disability

Asymptomatic Carrier n = 17
Healthy Volunteer n = 24
HAM/TSP n = 45
Increased disease duration, EDSS, and IPEC are associated with decrease in thoracic spinal cord cross sectional area.

Functional disability scales

- **Disease Duration**
  - Longer disease duration
  - Thinner
  - $p=0.035$

- **EDSS**
  - Increasing mobility aid
  - Decrease in SC CSA (T4-9 mm$^2$)
  - $p=0.009$

- **IPEC**
  - Increasing disability
  - Decrease in SC CSA (T4-9 mm$^2$)
  - $p=0.031$
Higher HTLV-1 Proviral load correlates with thinner spinal cord in HTLV-1 infection

Decrease in spinal cord cross sectional area associated with increased CD8+ T cells in the CSF

Thoracic cord cross section area vs. CD8+ T cells in CSF

Asymptomatic carrier

HAM/TSP

CSF HTLV-1 proviral load (%) vs. T4-9, CSA average (mm²)

$P = 0.005$

SC CSA (T4-9, mm²) vs. CD8+ T cell frequency

$P = 0.039$
Disease progression in HAM/TSP

- First signs of disease can occur months to years after infection
- Progression of disease can occur slowly or rapidly

Yoshihisa Yamano, Tamoo Sato; Frontiers in Microbiology, 2012
HAM/TSP - presented to NIH with an 8 year history of weakness in left leg, then dragging both feet. Repeated falls prompted medical evaluation and use of cane 2 years before the first scan at “Month 0”. Little or no clinical progression since then.
HAM/TSP - Patient noticed weakness in his legs as he worked on construction sites 7 months before “Month 0” scan. Between month 0 and month 7 patient progressed from using cane to being dependent on a wheelchair for all mobility. Rapid clinical progression seen.
Hypothesis: The neuroinflammatory process in the thoracic cord causes thoracic degeneration and retrograde axon degeneration (explaining no upper body involvement in HAM/TSP)
Summary
(Neuroimmunology of HAM/TSP)

Pathology:
Increased CD8+ T cells in lesions

Immunology:
Increased CD8+ T cells in periphery and CSF
Expanded CD8+ TCRB

Clinical:
Spinal cord atrophy associated with
increase in CD8+ T cells
Research of rare diseases
(HTLV-I – HAM/TSP)
(20 million people worldwide infected: how can a virus cause disease in only a subset of infected individuals?)

can inform understanding of common neurological disorders
(EBV- Multiple Sclerosis)
(95% of all people infected with EBV: how can a virus cause disease in only a subset of infected individuals?)
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