Published in final edited form as:

J Pediatr. 2009 November ; 155(5): 700–706. doi:10.1016/j.jpeds.2009.05.027.

Early neurologic abnormalities associated with human T-cell lymphotropic virus type 1 infection in a cohort of Peruvian children

Emily A. Kendall, A.B.¹, Elsa González, M.D.², Iván Espinoza, M.D.^{2,3}, Martín Tipismana, M.D.^{2,4}, Kristien Verdonck, M.D.^{2,6}, Daniel Clark, Ph.D.^{2,7}, Sten H. Vermund, M.D., Ph.D.¹, and Eduardo Gotuzzo, MD, FACP.^{2,5}

¹Institute for Global Health and Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

²Instituto de Medicina Tropical 'Alexander von Humboldt', Universidad Peruana Cayetano Heredia;

³Department of Pediatrics. Hospital Nacional Cayetano Heredia;

⁴Neurology Service. Hospital Nacional Cayetano Heredia;

⁵Department of Infectious, Tropical and Dermatological Diseases. Hospital Nacional Cayetano Heredia;

⁶Laboratorios de Investigación y Desarrollo (LID), Facultad de Ciencias y Filosofía; Universidad Peruana Cayetano Heredia, Lima, Perú

⁷Virology Unit, Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium

Abstract

Objective—Because human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) may occur in some children infected with HTLV-1-infected, we sought to determine the prevalence of neurologic abnormalities and any associations with infective dermatitis in these children.

Study design—We enrolled 58 children infected with HTLV-1 and 42 uninfected children (ages 3–17) of mothers infected with HTLV-1 in a family study in Lima, Peru. We obtained medical and developmental histories, surveyed current neurologic symptoms, and conducted a standardized neurologic examination without prior knowledge of HTLV-1 status.

Results—HTLV-1 infection was associated with reported symptoms of lower extremity weakness/fatigue (OR=6.1, CI:0.7–281), lumbar pain (odds ratio [OR] = 1.7, 95% confidence interval [CI]: 0.4–8), and paresthesia/dysesthesia (OR=2.6, CI:0.6–15.8). HTLV-1 infection was associated with lower-extremity hyperreflexia (OR=3.1, CI:0.8–14.2), ankle clonus (OR=5.0, CI:1.0–48.3), and extensor plantar reflex (OR undefined; $p = 0.2$). Among children infected HTLV-1, a history of

Corresponding Author: Emily A. Kendall, c/o Sten H. Vermund, MD, PhD, Vanderbilt Institute for Global Health, 2525 West End Avenue, Ste. 750, Nashville, TN 37203, emily.kendall@gmail.com, Direct: 615.343.4169, Fax: 615.343.7797.

Requests for reprints should be addressed to: Dr. Eduardo Gotuzzo, Director, Instituto de Medicina Tropical 'Alexander von Humboldt', Universidad Peruana Cayetano Heredia, Ave. Honorio Delgado 430, San Martín de Porres, Lima 31, Peru. egh@upch.edu.pe

Edited by SL and WFB

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

infective dermatitis was associated with weakness (OR=2.7, CI:0.3–33), lumbar pain (OR=1.3, CI: 0.2–8), paresthesia/dysesthesia (OR=2.9, CI:0.5–20), and urinary disturbances (OR=5.7, CI:0.5–290).

Conclusions—Abnormal neurologic findings were common in Peruvian children infected with HTLV-1, and several findings were co-prevalent with infective dermatitis. Pediatricians should monitor children infected with HTLV-1 for neurologic abnormalities.

Keywords not in title

Tropical Spastic Paraparesis; Infective dermatitis

Human T cell lymphotropic virus type 1 (HTLV-1) infection affects 10-20 million people worldwide and is endemic in parts of Japan, the Caribbean, Africa, Italy, and South America¹, including Peru². Seroprevalence rates exceed 1% in endemic regions³ and in high-risk subpopulations of nonendemic countries including the United States^{4,5}. Transmission can occur sexually, by blood transfusion or needle sharing, or from mother to child via breastfeeding. Infected individuals are at risk to develop severe diseases including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infective dermatitis associated with HTLV-1 (IDH)³.

HAM/TSP is a progressive, nonremitting spastic paraparesis with associated bladder dysfunction, constipation, and sensory symptoms⁶. It often develops slowly over a decade or more⁷; factors associated with relatively rapid progression include female sex⁶, age >50 years, and high proviral load⁸. It is an immune-mediated disease of the central nervous system, particularly the pyramidal tracts, whose pathogenesis may involve a virus-triggered autoimmune reaction or a by-stander effect of the cytotoxic destruction of adjacent infected T cells^{6,9}. In addition to the classic spastic paraparesis picture, other neurologic symptoms including isolated peripheral neuropathy, ataxia⁷, cognitive deficits⁹, myopathy and sympathetic dysautonomia⁶ are becoming recognized as part of a broader complex of HTLV-1-related neurologic disease.

Development of HAM/TSP most commonly follows sexual HTLV-1 transmission during adulthood and appears in the fourth or fifth decade of life¹⁰⁻¹². However, HAM/TSP also can occur following vertical HTLV-1 transmission during infancy, and multiple cases in children and adolescents are described¹³⁻²¹. A study of asymptomatic Jamaican children infected with HTLV-1 suggested hyperreflexia as an early HTLV-1-associated abnormality²². Despite these suggestive reports, the overall neurologic impact of HTLV-1 infection in children remains poorly defined due to the very small sample sizes and the limited scope of neurologic examinations in prior studies.

Case reports of HAM/TSP in children and adolescents, although varied, describe initial disease presentations that may include weakness, difficulty running, leg or back pain, and/or urinary incontinence^{14,15}. The course of disease progression in children can be atypically slow and erratic²³ or exceptionally rapid²⁰ compared with adults. The eventual outcome, however, is typical HAM/TSP clinical picture including weakness, spasticity, clonus, constipation, extensor plantar reflexes (Babinski sign), and occasionally finger flexor reflexes (Hoffman sign), other pyramidal signs, and sensory or cerebellar deficits^{14,15,24,25}.

A more commonly recognized health effect of HTLV-1 infection in children is a recurrent infected eczema, known as infective dermatitis associated with HTLV-1 (IDH)²⁶. IDH has been reported in association with both concurrent and later HAM/TSP^{14-16,21,27,28} and adult T-cell leukemia/lymphoma (ATLL)^{21,29,30}. One study diagnosed HAM/TSP in 6 of 20 children with infective dermatitis who underwent neurologic evaluation, although familial

clustering may have been a factor in that study population's high prevalence of neurologic disease¹⁴. Learning delay also has been reported in children with HTLV-1 infection in association with IDH and early HAM/TSP development¹⁵, although at least one small Peruvian study of early development found no significant differences between 10 children infected with HTLV-1 and 38 uninfected children studied³¹. Investigation of the link between IDH and HAM/TSP is ongoing. Both involve a proinflammatory microenvironment and dysregulated host-pathogen interactions, including activated but ineffective CD8+ T cells^{32,33}. Both IDH and HAM/TSP patients also have high levels of anti-HTLV-1 antibodies^{15,20}, which may reflect a high proviral load as a shared pathogenetic factor³⁴. In IDH, viral antigens and bacterial superantigens increase T-lymphocyte stimulation, enlarging the population of dividing cells that HTLV-1 can infect, and thereby increasing the possibility for other HTLV-related disease³⁵. Finally, in both instances of immune hyperactivation, human lymphocyte antigen (HLA) factors play a role, and certain HLA types have been identified as shared risk factors for both IDH and HAM/TSP^{33,36}.

In this study, we sought to examine the prevalence, as well as the association with IDH, of neurologic abnormalities in a cohort of Peruvian children with and without HTLV-1 infection.

Methods

We conducted standardized, blinded neurological evaluations of children with and without HTLV-1 infection of mothers infected with HTLV-1 in Lima, Peru, where the estimated prevalence of HTLV-1 infection in pregnant women is 1.7%³⁷. Study participants were drawn from an ongoing HTLV-1 family cohort study (n>600 families) at the Institute of Tropical Medicine "Alexander von Humboldt" in Lima², comprised primarily of families of patients who have visited or been referred to the hospital for HTLV-1-related illnesses, along with families of asymptomatic HTLV-1-infected blood donors. Children in these families were eligible if they were between 3 and 17 years of age and were born to an cohort participant with HTLV-1-infection. An attempt was made to contact all eligible cohort families living within the province of Lima by visiting their homes.

Study approval was obtained from the Institutional Ethics Committee of the Universidad Peruana Cayetano Heredia and the Institutional Review Board of Vanderbilt University. All participants and their parents or guardians received written and verbal explanations of study purpose and procedures, and parents/guardians gave written informed consent, and children gave age-appropriate assent.

Children and their mothers or other guardians were interviewed immediately following study enrollment by an interviewer (EAK) blinded to HTLV-1 infection status. The data gathered included age, sex, and grade in school; information about factors related to HTLV-1 transmission including peripartum events, past blood transfusions, and duration of breastfeeding; and family history of HTLV-1-associated diseases. Mothers/guardians were asked to recall the age of several early developmental milestones: crawling, walking, speaking, and cessation of diaper use. They also were queried about their child's medical history, including any HTLV-1-associated diseases (infective dermatitis – defined by previous physician's diagnosis or by clear description of the characteristic rash – as well as crusted scabies, *Strongyloides stercoralis* hyperinfection, or uveitis), any other illnesses or hospitalizations, and HIV infection status. Children (and/or their guardians for children less than 6 years old) also were queried about a set of symptoms often associated with HAM/TSP onset, as described by WHO guidelines³⁸ and recently revised diagnostic criteria³⁹: subjective lower extremity weakness or fatigability causing difficulty running or playing; paresthesias or dysesthesias in the lower extremities; radiating lumbosacral pain; bladder disturbances; and

constipation. Subjects or their guardians reported and described each symptom they experienced, and the interviewer assigned a 0-4 severity rating for each symptom.

Within 2 months following the initial interview, subjects visited our clinic for an evaluation by a neurologist (IE or MT). The neurological evaluation included a thorough history and examination. Children's height and weight were recorded, and a weight-for-age percentile was determined based on the U.S. Centers for Disease Control and Prevention year-2000 standard growth curves. For children under 6 years of age, a single examiner (EAK) also conducted the Denver Developmental Screening Test II (DDST).

HTLV-1 infection was determined by serum enzyme linked immunosorbent assay (ELISA). Positive ELISA results were repeated and then confirmed by either Western blot or line immunoassay, depending upon availability of reagents. Subjects with indeterminate results (N=3) were excluded from analysis.

To maintain a blinded evaluation, the interviewer and neurologists were unaware of children's HTLV-1 infection status. Medical records were unavailable to them prior to the interview/exam; the patients were unfamiliar to them; and parents/guardians and subjects were instructed not to reveal children's infection status, if known, to the research personnel. Serum samples were collected and analyzed by staff without knowledge of infection status or interview/exam results. Data were linked to HTLV-1 serostatus by a third party after all evaluations were completed, with personal identifiers removed to ensure confidentiality.

Statistical methods

Population characteristics were analyzed with Fisher exact tests (with two-tailed *p* values) or unpaired t-tests as appropriate. Fisher exact tests were used to test for associations between infection and neurologic symptoms, and between infection and neurological exam findings, with one-tailed *p* values; two-tailed *p* values were determined for associations between neurologic signs/symptoms and infective dermatitis history. Ninety-five percent exact confidence intervals for odds ratios were computed. A minimum severity score of 2 out of 4 was taken to represent a significant positive neurologic symptom, although trends are similar when other cut-offs are used. Because of non-normality, the Wilcoxon-Mann-Whitney rank-sum test was used to test for associations between infection status and ages of attainment of developmental milestones.

Results

According to records for >600 HTLV-1 cohort families, 104 families had children eligible for this study. Of these, 66 families were reached and agreed to participate, ultimately yielding 103 eligible study participants from 63 families: 58 children were infected with HTLV-1 and 42 children were uninfected (and 3 excluded based on indeterminate serological results). None had previously-recognized HAM/TSP. Age and sex profiles are similar for HTLV-1-infected and uninfected subject groups (Table I). Almost all children in both groups were breastfed, but children with HTLV-1 infection breastfed until a later age ($p=0.02$). No children reported blood transfusions or sexual activity prior to HTLV-1 diagnosis. Nearly all mothers had been HIV-tested in pregnancy and none were HIV-infected; many children also had confirmed HIV-negative serologies. Infected subjects were slightly more likely to have been born prematurely and/or required extended hospital stays as neonates, and also had somewhat lower weights for their age (Table I).

Some participants only completed one of the two major portions of the study; 96 were interviewed and 75 examined. There were no significant differences between participants with complete and incomplete data. Of the 63 families who had children included in analysis, 9

families contributed 3 participants each (all but 1 of these families contributing both infected and uninfected participants), and 19 families contributed 2 participants each (with concordant infection status in 10, discordant in 9). The remaining 35 participants did not have siblings in the study.

Children infected with HTLV-1 reported leg weakness, lumbar pain, paresthesias/dysesthesias, urinary incontinence, and constipation more frequently than uninfected children (Table II). Both clonus and lower extremity hyperreflexia were significantly associated with HTLV-1 infection. Most children with any neurologic exam abnormality had lower extremity hyperreflexia, with or without some additional abnormality. Extensor plantar reflex, finger flexor reflex, lower extremity weakness, fasciculations, cranial nerve signs, and cerebellar syndrome were also found exclusively in children infected with HTLV-1, although these findings were infrequent and not associated with statistical significance (Table III).

Two study participants, both teenage females, were diagnosed with HAM/TSP by study neurological evaluations. One was a 17-year-old girl with symptoms of constipation and urinary incontinence that had progressed over the previous 2 years to profound patellar hyperreflexia, diminished Achilles tendon reflexes, lower extremity spasticity, lower extremity weakness, bilateral clonus and extensor plantar reflex, and a sensory deficit (diminished fine touch and vibratory sensation below T8). The other was a 16-year-old girl reporting recent-onset lumbar pain, subjective weakness, paresthesias, urinary urgency, and frequent constipation; exam revealed bilateral lower extremity hyperreflexia, clonus, and extensor plantar reflexes.

Of the 53 HTLV-1-infected study participants whose dermatologic histories were obtainable, 23 (43%) reported infective dermatitis. There was a weak positive association between IDH and each neurologic abnormality for except clonus and constipation (Table IV).

Neurodevelopmental milestones, as based on parental or guardian recall, did not differ between children with and without HTLV-1 infection. Median age for crawling was 8 months for children both infected and uninfected; for walking, 12 months for both groups; for first word, 9 months for infected and 10 months for uninfected groups; and for potty training, 18 months in both groups ($p > 0.7$ for all comparisons).

The Denver Developmental Screening Test II was also conducted for children less than 6 years of age. The sample size is too small to allow substantial analysis: 7 children with infection and 6 children uninfected in the appropriate age range. However, delayed performances meriting “failures” and “cautions” appeared to occur more frequently in the infected group for all categories of the test (fine motor, gross motor, language, and personal-social). Differences were notable in gross motor skills (3 cautions and 4 normal performances in the infected group, 6 normal in the uninfected group, $p = 0.07$).

Discussion

We found that childhood HTLV-1 infection was associated with lower pyramidal tract signs and neuromuscular symptoms consistent with early HAM/TSP. Nearly all of the signs and symptoms considered were present more frequently in children with infection, and, although differences for some infrequent findings may have been due to chance, overall there is a significant association of infection with an abnormal examination. The association of HTLV-1 infection with lower extremity hyperreflexia is consistent with the previously-mentioned Jamaican study²², although the prevalence of hyperreflexia at a single time point in our participants (34% among infected, 14% among uninfected) was higher than the prevalence of persistent hyperreflexia (8% among infected, 2% among uninfected children) found in Jamaica.

More than half of study participants were infected with HTLV-1. This is higher than the usual prevalence of HTLV-1 infection among offspring of infected mothers. The predominance of infected status may be due in part to the long average duration of breast feeding in our population, which as expected is highest for children infected with HTLV-1. The predominance also may reflect symptom-related detection of infection in children and higher rates of vertical transmission from mothers with HTLV-associated diseases. Although none of our participants presented for medical care because of neurologic symptoms, many did present and were enrolled into our cohort because they had IDH. Others were enrolled because their mothers had diseases such as HAM/TSP or ATLL, which reflect a high maternal proviral load and a higher risk of transmission via breast feeding⁴⁰⁻⁴³. A limitation of our study is the absence of full neurological exams of the mothers; we cannot comment on whether HAM/TSP in a mother predicted neurologic abnormalities in her children.

With respect to early childhood development, the similarity between infected and uninfected groups may indicate that the infected group was not notably disadvantaged prior to infection, despite having a higher percentage of preterm births, neonatal hospitalizations, and low childhood weight. Peripartum transmission occurs in <5% of pregnancies^{44,45} and transmission rates to children breastfed <6 months are similarly around 5%, possibly because of protective maternally-acquired antibodies^{41,46-48}, whereas transmission exceeds 30% for children breastfed >1 year^{40,49}. Therefore, these early milestones are attained before most subjects are likely to have become infected. Our finding of poorer DDST performance in children with infection, particularly in gross motor skills, would be consistent with neurologic effects of HTLV-1 on somewhat later childhood development, but our sample size is too small to permit conclusions.

If children with HTLV-1-infection are at an increased risk for neurologic or psychomotor abnormalities, it would be helpful to identify indicators of children most at risk. The weak positive associations we found between IDH and subjective weakness, lumbar pain, paresthesia, and urinary incontinence – often some of the first symptoms noted in cases of childhood HAM/TSP – as well as with most abnormal neurological exam findings, are consistent with previous reports¹⁴⁻¹⁶ suggesting IDH as such a risk indicator. Given that HAM/TSP most often affects adult women, we also considered age and sex as risk factors for developing neurologic disability in the context of HTLV-1 infection. Symptoms and abnormal examinations were positively correlated with age, but the correlations were weak and none are statistically significant (spearman's $\rho \leq 0.3$, p values 0.1-0.8). There was no consistent trend associating sex with abnormal symptoms or signs. We note, however, that the two participants most severely affected were relatively older females.

We believe we have minimized several potential sources of bias in our study. Our children with and without HTLV-1 infection were quite similar in overall demographic profile, and we believe that including children whose mothers had confirmed HTLV-1 infection helped control for any potential sociodemographic contributions to disease. Clustering of HAM/TSP within families has been observed previously^{15,50,51}. However, the large number of distinct families participating in our study and the even distributions of most siblings between cohort groups would reduce effects of familial clustering of abnormalities. Although investigators were blinded, many participants and/or their guardians knew their infection status, but as reports of early developmental milestones were not associated with infection status, we do not think that this knowledge biased the reporting of symptoms. We recognize the possibility of seronegative paraparesis, caused by incomplete or defective HTLV-1 proviruses that have been detected inconsistently in seronegative patients with HAM/TSP-like clinical disease⁵²⁻⁵⁵, occurring within our HTLV-1 “uninfected” group. This would result in a higher-than-expected frequency of abnormalities in uninfected children and decrease the statistical power of our study to find

differences between the infected and uninfected children, but this would not reverse any positive findings.

Our sample size of 58 children with infection and 42 children without infection (with incomplete examinations of many subjects) is a notable limitation, precluding substantial analysis. Data will be useful for future meta-analysis to combine data from multiple cohorts, assuming that neurologic assessments are blinded and conducted with methodologic symmetry across surveys.

Our study suggests that children and adolescents infected with HTLV-1 are at significant risk for developing HAM/TSP-like neurologic abnormalities. Early clinical evaluation may identify otherwise-unrecognized neurologic disease in infected children, as has been possible in adults⁵⁶. Frequent screening of children infected with HTLV-1 for neurologic abnormalities is important, because the best window for intervention appears to be in the first year of disease⁵⁷, and also because children may benefit from symptomatic treatment of neuropathy or spasticity as well as from psychosocial support. The link with infective dermatitis may be useful as a clinical marker for children most at risk. However, because children with and without history of IDH were affected in our study, all children with HTLV-1 infection require neurologic monitoring. The frequency at which infected children appear to be neurologically affected also highlights the need for prevention of vertical transmission, particularly through elimination or reduction in duration of breast feeding. Most importantly for infected children is to discover antiretroviral drugs, immunomodulatory strategies, or other therapies that, if applied early, might delay or prevent disease progression.

Acknowledgments

We thank health care field workers Viviana Quintana and Yessica Ramos, RN for their substantial assistance in home visits, and Joe Zunt, MD, for helpful suggestions on the manuscript.

This study supported by the Directorate-General for Development Cooperation of the Belgian Government through a Framework Agreement with the Institute of Tropical Medicine in Antwerp (DGOS-II); the Flemish Interuniversity Council Programme (VLIR); Vanderbilt University School of Medicine Emphasis Program; the Vanderbilt-Meharry Center for AIDS Research (NIH grant #P30AI054999); and the Vanderbilt-Meharry Framework Program for Global Health (NIH grant #R25TW007766). The authors declare no potential conflicts of interest.

List of abbreviations used

HTLV-1	human T-cell lymphotropic virus type 1
HAM/TSP	HTLV-1-associated myelopathy/tropical spastic paraparesis
IDH	Infective dermatitis associated with HTLV-1
ATLL	Adult T-cell Leukemia/Lymphoma
HLA	human lymphocyte antigen
CI	confidence interval
OR	odds ratio

ELISA

enzyme linked immunosorbent assay

DDST

Denver Developmental Screening Test

References

1. Edlich RF, Arnette JA, Williams FM. Global epidemic of human T-cell lymphotropic virus type-I (HTLV-I). *J Emerg Med* 2000;18:109–119. [PubMed: 10645850]
2. Gotuzzo E, Arango C, de Queiroz-Campos A, Istúriz RE. Human T-cell lymphotropic virus-I in Latin America. *Infect Dis Clin North Am* 2000;14:211–239. x–xi. [PubMed: 10738680]
3. Verdonck K, González E, Van Dooren S, Vandamme A, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *The Lancet Infectious Diseases* 2007;7:266–281. [PubMed: 17376384]
4. Robert-Guroff M, Weiss SH, Giron JA, Jennings AM, Ginzburg HM, Margolis IB, et al. Prevalence of antibodies to HTLV-I, -II, and -III in intravenous drug abusers from an AIDS endemic region. *JAMA* 1986;255:3133–3137. [PubMed: 3009910]
5. Kelen GD, DiGiovanna TA, Lofy L, Junkins E, Stein A, Sivertson KT, et al. Human T-lymphotropic virus (HTLV I-II) infection among patients in an inner-city emergency department. *Ann Intern Med* 1990;113:368–72. [PubMed: 2382919]
6. Araujo AQC, Silva MTT. The HTLV-I neurological complex. *Lancet Neurology* 2006;5:1068–1076. [PubMed: 17110288]
7. Carod-Artal FJ, Mesquita HM, Ribeiro LDS. Neurological symptoms and disability in HTLV-I associated myelopathy. *Neurologia* 2008;23:78–84. [PubMed: 18322825]
8. Olindo S, Cabre P, Lézin A, Merle H, Saint-Vil M, Signate A, et al. Natural history of human T-lymphotropic virus 1-associated myelopathy: a 14-year follow-up study. *Arch Neurol* 2006;63:1560–1566. [PubMed: 17101824]
9. Nakamura T. Immunopathogenesis of HTLV-I-associated myelopathy/tropical spastic paraparesis. *Ann Med* 2000;32:600–607. [PubMed: 11209967]
10. Gotuzzo E, Cabrera J, Deza L, Verdonck K, Vandamme A, Cairampoma R, et al. Clinical characteristics of patients in Peru with human T cell lymphotropic virus type 1-associated tropical spastic paraparesis. *Clin Infect Dis* 2004;39:939–944. [PubMed: 15472843]
11. Maloney EM, Cleghorn FR, Morgan OS, Rodgers-Johnson P, Cranston B, Jack N, et al. Incidence of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Jamaica and Trinidad. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:167–170. [PubMed: 9473019]
12. Krämer A, Maloney EM, Morgan OS, Rodgers-Johnson P, Manns A, Murphy EL, et al. Risk factors and cofactors for human T-cell lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Jamaica. *Am J Epidemiol* 1995;142:1212–1220. [PubMed: 7485068]
13. Zaninovic V. Tropical spastic paraparesis. *Lancet* 1987;2:280. [PubMed: 2886749]
14. Araújo APQC, Fontenelle LMC, Pádua PAB, Maia Filho HS, Araújo ADQC. Juvenile human T lymphotropic virus type 1-associated myelopathy. *Clin Infect Dis* 2002;35:201–204. [PubMed: 12087528]
15. Primo JRL, Brites C, Oliveira MDFSPD, Moreno-Carvalho O, Machado M, Bittencourt AL. Infective dermatitis and human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis in childhood and adolescence. *Clin Infect Dis* 2005;41:535–541. [PubMed: 16028164]
16. de Oliveira MDFSP, Bittencourt AL, Brites C, Soares G, Hermes C, Almeida FO. HTLV-I associated myelopathy/tropical spastic paraparesis in a 7-year-old boy associated with infective dermatitis. *J Neurol Sci* 2004;222:35–38. [PubMed: 15240193]
17. LaGrenade L, Morgan C, Carberry C, Hanchard B, Fletcher V, Gray R, et al. Tropical spastic paraparesis occurring in HTLV-1 associated infective dermatitis. Report of two cases. *West Indian Med J* 1995;44:34–35. [PubMed: 7793113]

18. Osame M, Igata A, Usuku K, Rosales RL, Matsumoto M. Mother-to-child transmission in HTLV-I associated myelopathy. *Lancet* 1987;1:106. [PubMed: 2879161]
19. Quintas S, Moreno T, Lobo-Antunes N, Levy-Gomes A. Tropical spastic paraparesis and HTLV-I associated myelopathy in infancy. A case report and review of the literature. *Rev Neurol* 39:1133–1136. [PubMed: 15625631]
20. Bittencourt AL, Primo J, Oliveira MFPD. Manifestations of the human T-cell lymphotropic virus type I infection in childhood and adolescence. *J Pediatr (Rio J)* 2006;82:411–420. [PubMed: 17171202]
21. Farre L, de Oliveira MDPF, Primo J, Vandamme A, Van Weyenbergh J, Bittencourt AL. Early sequential development of infective dermatitis, human T cell lymphotropic virus type I-associated myelopathy, and adult T cell leukemia/lymphoma. *Clin Infect Dis* 2008;46:440–442. [PubMed: 18173359]
22. Maloney EM, Wiktor SZ, Palmer P, Cranston B, Pate EJ, Cohn S. A cohort study of health effects of human T-cell lymphotropic virus type I infection in Jamaican children. *Pediatrics* 2003;112:e136–142. [PubMed: 12897319]
23. Nakagawa M, Izumo S, Ijichi S, Kubota H, Arimura K, Kawabata M, et al. HTLV-I-associated myelopathy: analysis of 213 patients based on clinical features and laboratory findings. *J Neurovirol* 1995;1:50–61. [PubMed: 9222342]
24. Carod-Artal FJ, del Negro MC, Vargas AP, Rizzo I. Cerebellar syndrome and peripheral neuropathy as manifestations of infection by HTLV-1 human T-cell lymphotropic virus. *Rev Neurol* 1999;29:932–935. [PubMed: 10637843]
25. Román GC, Osame M. Identity of HTLV-I-associated tropical spastic paraparesis and HTLV-I-associated myelopathy. *Lancet* 1988;1:651.
26. LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet* 1990 Dec 1;336(8727):1345–7. [PubMed: 1978165]
27. La Grenade L. HTLV-I, infective dermatitis, and tropical spastic paraparesis. *Mol Neurobiol* 8(23): 147–53. [PubMed: 7999311]
28. Oliveira MDPSPD, Brites C, Ferraz N, Magalhaes P, Almeida F, Bittencourt AL. Infective dermatitis associated with the human T cell lymphotropic virus type I in Salvador, Bahia, Brazil. *Clin Infect Dis* 2005;40:e90–96. [PubMed: 15889351]
29. Kaplan JE, Osame M, Kubota H, Igata A, Nishitani H, Maeda Y, et al. The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. *J Acquir Immune Defic Syndr* 1990;3:1096–1101. [PubMed: 2213510]
30. Bittencourt AL, Oliveira MDF, Brites C, Van Weyenbergh J, da Silva Vieira MDG, Araújo I. Histopathological and immunohistochemical studies of infective dermatitis associated with HTLV-I. *Eur J Dermatol* 2005;15:26–30. [PubMed: 15701589]
31. Montano SM, Zunt JR, Rodriguez L, Quispe I, Rodriguez C, Altamirano J, et al. Human T cell lymphotropic virus type I infection and early neurologic development: a pilot study of 48 children. *Clin Infect Dis* 2004;39:1079–1082. [PubMed: 15472866]
32. Goncalves DU, Proietti FA, Barbosa-Stancioli EF, Martins ML, Ribas JG, Martins-Filho OA. HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) inflammatory network. *Inflamm Allergy Drug Targets* 2008;7:98–107. [PubMed: 18691139]
33. Matsuoka M. Human T-cell leukemia virus type I (HTLV-I) infection and the onset of adult T-cell leukemia (ATL). *Retrovirology* 2005;2:227.
34. Shinzato O, Kamihira S, Ikeda S, Kondo H, Kanda T, Nagata Y. Relationship between the anti-HTLV-1 antibody level, the number of abnormal lymphocytes and the viral-genome dose in HTLV-1-infected individuals. *Int J Cancer* 1993;54:208–212. [PubMed: 8098012]
35. Tschachler E, Franchini G. Infective Dermatitis: A Pabulum for Human T-Lymphotropic Virus Type I Leukemogenesis? *Arch Dermatol* 1998;134:487–488. [PubMed: 9554302]
36. LaGrenade L, Sonoda S, Miller W, Pate E, Rodgers-Johnson P, Hanchard B, et al. HLA DRB1*0401 haplotype in HTLV-I-associated familial infective dermatitis may predict development of HTLV-I-associated myelopathy/tropical spastic paraparesis. *Am J Med Genet* 1996;61:37–41. [PubMed: 8741915]

37. Alarcón JO, Friedman HB, Montano SM, Zunt JR, Holmes KK, Quinnan GV. High endemicity of human T-cell lymphotropic virus type 1 among pregnant women in Peru. *J Acquir Immune Defic Syndr* 2006;42:604–609. [PubMed: 16773029]
38. Scientific Group on HTLV-I Infections and Associated Diseases: report. World Health Organization (WHO); Manila: WHO; 1989.
39. De Castro-Costa CM, Araújo AQC, Barreto MM, Takayanagui OM, Sohler MP, da Silva ELM, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM). *AIDS Res Hum Retroviruses* 2006;22:931–935. [PubMed: 17067261]
40. Gotuzzo E, Moody J, Verdonck K, Cabada MM, González E, Van Dooren S, et al. Frequent HTLV-I infection in the offspring of Peruvian women with HTLV-I-associated myelopathy/tropical spastic paraparesis or strongyloidiasis. *Rev Panam Salud Publica* 2007;22:223–230. [PubMed: 18078583]
41. Ureta-Vidal A, Angelin-Duclos C, Tortevoe P, Murphy E, Lepère JF, Buigues RP, et al. Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. *Int J Cancer* 1999;82:832–836. [PubMed: 10446450]
42. Li H, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B, et al. Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. *J Infect Dis* 2004;190:1275–1278. [PubMed: 15346338]
43. Maloney EM, Hisada M, Palmer P, Brooks K, Pate E, Wiktor SZ, et al. Human T cell lymphotropic virus type I-associated infective dermatitis in Jamaica: a case report of clinical and biologic correlates. *Pediatr Infect Dis J* 2000;19:560–565. [PubMed: 10877174]
44. Fujino T, Nagata Y. HTLV-I transmission from mother to child. *J Reprod Immunol* 2000;47:197–206. [PubMed: 10924751]
45. Bittencourt AL, Sabino EC, Costa MC, Pedrosa C, Moreira L. No evidence of vertical transmission of HTLV-I in bottle-fed children. *Rev Inst Med Trop Sao Paulo* 2002;44:63–65. [PubMed: 12048541]
46. Takezaki T, Tajima K, Ito M, Ito S, Kinoshita K, Tachibana K, et al. Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. The Tsushima ATL Study Group. *Leukemia* 1997;11:s360–362.
47. Oki T, Yoshinaga M, Otsuka H, Miyata K, Sonoda S, Nagata Y. A sero-epidemiological study on mother-to-child transmission of HTLV-I in southern Kyushu, Japan. *Asia Oceania J Obstet Gynaecol* 1992;18:371–377. [PubMed: 1362873]
48. Takahashi K, Takezaki T, Oki T, Kawakami K, Yashiki S, Fujiyoshi T, et al. Inhibitory effect of maternal antibody on mother-to-child transmission of human T-lymphotropic virus type I. The Mother-to-Child Transmission Study Group. *Int J Cancer* 1991;49:673–677. [PubMed: 1937953]
49. Wiktor SZ, Pate EJ, Rosenberg PS, Barnett M, Palmer P, Medeiros D, et al. Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. *J Hum Virol* 1997;1:37–44. [PubMed: 10195229]
50. Pombo-de-Oliveira MS, Carvalho SM, Borducchi D, Dobbin J, Salvador J, Correa RB, et al. Adult T-cell leukemia/lymphoma and cluster of HTLV-I associated diseases in Brazilian settings. *Leuk Lymphoma* 2001;42:135–144. [PubMed: 11699201]
51. Adaui V, Verdonck K, Best I, González E, Tipismana M, Arévalo J, et al. SYBR Green-based quantitation of human T-lymphotropic virus type 1 proviral load in Peruvian patients with neurological disease and asymptomatic carriers: influence of clinical status, sex, and familial relatedness. *J Neurovirol* 2006;12:456–465. [PubMed: 17162661]
52. Ramirez E, Fernandez J, Cartier L, Villota C, Rios M. Defective human T-cell lymphotropic virus type I (HTLV-I) provirus in seronegative tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM) patients. *Virus Res* 2003;91:231–239. [PubMed: 12573502]
53. Nagai M, Utsunomiya T, Takenouchi N, Izumo S, Osame M. Failure to detect HTLV type 1 DNA from HTLV type 1-seronegative patients with chronic progressive spastic paraparesis in Kagoshima. *AIDS Res Hum Retroviruses* 2002;18:1089–1090. [PubMed: 12396460]
54. Costa CM, Goubau P, Liu HF, Vandamme AM, da Cunha FM, Santos TJ, et al. HTLV-negative and HTLV type I-positive tropical spastic paraparesis in northeastern Brazil AIDS. *Res Hum Retroviruses* 1995;11:315–318.

55. Castro-Costa CM, Carton H, Santos TJ. HTLV-I negative tropical spastic paraparesis: a scientific challenge. *Arq Neuropsiquiatr* 2001;59:289–294. [PubMed: 11400047]
56. Lima MA, Harab RC, Schor D, Andrada-Serpa MJ, Araújo AQC. Subacute progression of human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis. *J Neurovirol* 2007;13:468–473. [PubMed: 17994432]
57. Araújo AQ, Leite AC, Dutra SV, Andrada-Serpa MJ. Progression of neurological disability in HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *J Neurol Sci* 1995;129:147–151. [PubMed: 7608729]

Table 1
Demographic and perinatal characteristics of enrolled study subjects.

	HTLV-1 infected (58)	HTLV-1 uninfected (42)	P
Age			
mean±SD	10.7 ± 3.8	11.3 ± 4.2	0.5
interquartile range	(8.5, 12.8)	(7.5, 14.7)	
Sex (male:female)	38%:62% (22:36)	43%:57% (18:24)	0.7
Cesarean deliveries	9% (5/55)	10% (4/42)	1.0
Preterm Births	20% (11/54)	12% (5/41)	0.4
Neonatal Hospitalizations	18% (10/55)	12% (5/42)	0.6
Breastfed	96% (52/54)	98% (41/42)	1.0
Months of breastfeeding	22.4 ± 16.2	15.5 ± 9.5	0.02
Underweight-for-age [*] :			
<25th percentile	41% (17/41)	17% (4/24)	0.05
< 10th percentile	29% (12/41)	17% (4/24)	0.4
<5th percentile	17% (7/41)	8% (2/24)	0.5

^{*}Based on CDC year-2000 standard growth curves

Table 2

Reports of neurologic symptoms commonly associated with HAM/TSP, by 55 children infected with HTLV-1 and 42 children uninfected with HTLV ages 3-17 in Lima, Peru.

	Infected (N=55)	Uninfected (N=42)	P	OR (95% CI)
Weakness or difficulty running/walking	7 (13%)	1 (2%)	0.026	1 (0.7 – 281)
Lumbar pain	8 (15%)	4 (10%)	0.091	1.7 (0.4 – 8)
Urinary incontinence, retention, or urgency	7 (13%)	5 (12%)	0.1	1.1 (0.3 – 5)
Constipation	10 (19%)	7 (17%)	0.2	1.1 (0.3 – 4)
Paresthesias or dysesthesias	9 (17%)	3 (7%)	0.072	2.6 (0.6 – 15.8)

Table 3
Neurologic exam findings in 47 children infected with HTLV-1 and 28 children uninfected.

	Infected (N=47)	Uninfected (N=28)	P	OR (95% CI)
Upper motor neuron abnormalities				
Lower extremity hyperreflexia	16 (34%)	4 (14%)	0.053	3.1 (0.8 – 14.2)
Clonus	13 (28%)	2 (7%)	0.035	5.0 (1.0 – 48.3)
Extensor plantar reflex	3 (6%)	0	0.2	†
Finger flexor reflex	1 (2%)	0	*	†
Other neurological findings				
Diminished lower extremity strength	3 (6%)	0	0.2	†
Cranial nerve signs	1 (2%)	0	*	†
Cerebellar syndrome	3 (6%)	0	0.2	†
Fasciculations	1 (2%)	0	*	†
Tremor	1 (2%)	1 (3%)	*	*
Tactile sensory deficit	1 (2%)	0	*	†
Any of the above abnormalities	19 (40%)	5 (18%)	0.04	3.1 (1.0 – 9.3)

* not calculated due to infrequency of finding

† OR (odds ratio) undefined

Table 4

Neurologic symptoms and abnormal exam findings in 48 children infected with HTLV-1 with and without histories of HTLV-1-related infective dermatitis

	History of infective dermatitis N=23	No history of infective dermatitis N=28	P	OR (95% CI)
Reported symptoms of:				
Weakness	4 (17%)	2 (7%)	0.3	2.7 (0.3 – 33)
Lumbar pain	4 (17%)	4 (14%)	0.9	1.3 (0.2 – 8)
Urinary incontinence	4 (17%)	1 (4%)	0.2	5.7 (0.5 – 290)
Paresthesia/dysesthesia	6 (26%)	3 (11%)	0.2	2.9 (0.5 – 20)
Exam finding of:	N=18	N=23		
Lower extremity hyperreflexia	6 (33%)	7 (30%)	>0.9	1.1 (0.2 – 5)
Clonus	4 (22%)	6 (26%)	>0.9	*0.8 (0.1 – 4)
Lower extremity weakness	2 (11%)	1 (4%)	0.6	2.8 (0.1 – 162)
Cerebellar syndrome	2 (11%)	1 (4%)	0.6	2.8 (0.1 – 162)
Extensor plantar reflex	1 (6%)	1 (4%)	>0.9	1.3 (0.01 – 106)
Any abnormal exam finding other than hyperreflexia/clonus	5 (28%)	3 (13%)	0.3	2.6 (0.4 – 19)

* Slightly more prevalent in children with no IDH history