Infective Dermatitis and Human T Cell Lymphotropic Virus Type 1–Associated Myelopathy/Tropical Spastic Paraparesis in Childhood and Adolescence

Janeusa Rita L. Primo,[1] Carlos Brites,[1] Maria de Fátima S. P. de Oliveira,[1] Otávio Moreno-Carvalho,[1] Marcos Machado,[3] and Achiléa L. Bittencourt[2]

Departments of [1]Medicine and [2]Pathology, Federal University of Bahia, and [3]Department of Bioimage, São Rafael Hospital, Salvador, Bahia, Brazil

(See the editorial commentary by Hanchard on pages 542–3)

Background. Human T cell lymphotropic virus type 1 (HTLV-1)–associated infective dermatitis (IDH) is a chronic and recurrent eczema occurring during childhood and adolescence. HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic myelopathy of adulthood, presenting with slowly progressive spastic paraparesis and sphincter dysfunction with mild sensory involvement. There are few reports describing an association between IDH and HAM/TSP. The objective of this study was to evaluate the occurrence of HAM/TSP in patients with IDH and in seropositive members of their families and to determine the blood levels of antibodies against HTLV-1 in patients with HAM/TSP.

Methods. Twenty patients with IDH and their seropositive mothers and siblings underwent clinical, neurological, and laboratory evaluations. The diagnosis of HAM/TSP was made in accordance with the World Health Organization criteria.

Results. Nine individuals had HAM/TSP (6 of the patients with IDH, 2 mothers, and 1 seropositive brother). In 3 families, >1 individual had HAM/TSP. The serum antibody titers of the patients with HAM/TSP varied from 1:3.125 to 1:78.125.

Conclusions. A strong association was observed between IDH and HAM/TSP. The familial clustering of both diseases suggests a genetic background. Serological screening for HTLV-1 in children with symptoms of myelopathy is essential in areas where HTLV-1 is endemic.

Carriers of the human T cell lymphotropic virus type 1 (HTLV-1) may develop severe diseases, including HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infective dermatitis associated with HTLV-1 (IDH) [1, 2]. HTLV-1 infection is endemic to southern Japan, the Caribbean, Africa, and South America, including Brazil. In Bahia, a state in the northeast of Brazil in which the population is predominantly of African and European descent, the mean prevalence of HTLV-1 infection is 1.35% among blood donors [3], 0.84% among pregnant women [4], and 1.76% among the general population [5]. The majority of infected people are asymptomatic carriers; however, ~5% may develop associated diseases [6].

IDH is a chronic and severe form of childhood dermatitis characterized by an exudative, infective dermatitis involving mainly the scalp, neck, and ears. Other symptoms include a generalized papular rash, nasal discharge, and crusting of the nostrils. The majority of patients with IDH who have been described are from Jamaica, and these patients were vertically infected [7, 8].

HAM/TSP is a myelopathy of insidious onset characterized by bladder disturbance, mild sensory involvement, and slowly progressive spastic paraparesis that mainly affects the pyramidal tracts. Symptoms usually appear during the fourth or fifth decade of life. How-

Received 26 January 2005; accepted 25 March 2005; electronically published 8 July 2005.

Reprints or correspondence: Dr. Janeusa Rita Leite Primo Chagas, Curso de Pós-Graduação em Medicina e Saúde da Faculdade de Medicina da Bahia da UFBA, Rua Padre Feijó, 240, Ambulatório Magalhães Neto, 3° Andar-Canela, Salvador, 40.110-170, Bahia, Brazil (janeusa.primo@cpunet.com.br).

Clinical Infectious Diseases 2005; 41:535–41

1058-4838/2005/4104-0019$15.00

ever, some patients may experience an acute or a subacute onset of the disease, followed by a rapid deterioration in their clinical condition [9, 10]. This rapid clinical evolution generally occurs in patients aged >60 years [10]. There have been well-documented reports of 10 cases of HAM/TSP occurring during childhood and adolescence, 6 of which were associated with IDH [11–15]. One of these cases is included in the present series. The main objective of the present study was to assess the occurrence of HAM/TSP in a series of 20 patients with IDH and in their seropositive mothers and siblings.

MATERIALS AND METHODS

Study population. Between October 2002 and November 2004, 20 patients with IDH and 25 seropositive family members (16 mothers and 9 siblings) were evaluated for neurological disorders. The patients were selected from the 23 patients diagnosed with IDH at the dermatology clinic of the School Hospital of the Federal University of Bahia (Bahia, Brazil) prior to 2002 [16] and referred to the neuropediatric clinic of the same hospital. Seventeen of those patients presented for follow-up at the clinic, and another 3 patients with IDH were later recruited from the clinic (table 1).

IDH was diagnosed in accordance with previously established criteria [7]. Of a total of 30 siblings (age, 1.6–18 years), only 23 presented to the clinic, and 9 of those persons were seropositive. Only 16 mothers of 20 patients with IDH were neurologically evaluated, because the study included 2 pairs of siblings with IDH, 1 child was abandoned at birth, and another mother was seronegative (her child had previously undergone a blood transfusion). All subjects were from families of low socioeconomic status. The median age of the patients with IDH was 11 years, the median age of the siblings was 14 years, and the median age at which diagnosis of IDH was made was 8 years. The patients had all been breast-fed, and the median duration of breast-feeding was 2 years. The patients were seropositive for HTLV-1 by ELISA testing (ELISA Kit; MUREX), and the diagnosis was confirmed by a Western blot that was capable of discriminating between HTLV-1 and -2 (HTLV Blot; Genelabs). Obstetric and clinical data on the study population were collected. Mothers or guardians were asked about the developmental milestones of the children. The study was approved by the Institutional Review Board of the School Hospital of the Federal University of Bahia, and informed consent was obtained from each child's mother or guardian.

Clinical and neurological examinations. A general clinical examination was performed for all patients. Ophthalmologic examination was performed for patients with visual complaints. The contour curve of the children's growth was determined in accordance with the percentiles established by the National Center for Health Statistics.

Table 1. Characteristics of and findings for the 20 patients with infective dermatitis associated with human T cell lymphotropic virus type 1 (HTLV-1).

Patient	Age in years, sex	Race	Duration of breast-feeding, years	Hemoglobin level, g/dL	Antibody titer
1[a]	8, M	Mixed race	3.0	10.5	1:3.125
2[a]	14, F	Black	1.8	10.3	1:15.625
3[a]	12, F	Mixed race	1.8	11.3	1:78.125
4[a]	12, F	Black	3.5	11.7	1:78.125
5[a]	9, F	Black	4.0	10.8	1:3.125
6[a]	12, F	Mixed race	0.7	10.5	1:2.799
7	8, F	Mixed race	4.9	11.6	1:78.125
8	7, F	Mixed race	0.2	12.6	…
9	13, F	Mixed race	1.2	11.3	…
10	13, M	Mixed race	1.0	13.0	1:625
11	14, F	Black	2.0	12.9	…
12	9, M	Mixed race	1.0	11.2	1:3.125
13	14, M	Mixed race	2.0	11.2	…
14	15, F	Mixed race	…	10.9	1:1.296
15	9, F	Mixed race	3.0	12.0	…
16	4, M	Mixed race	3.0	11.5	1:67.962
17	9, M	Mixed race	1.0	11.1	…
18	10, F	Mixed race	0.5	11.4	…
19	14, M	Mixed race	4.0	14.4	…
20	10, M	Mixed race	3.0	12.7	1:4.6456

[a] Patient also had HTLV-1–associated myelopathy/tropical spastic paraparesis.

Table 2. Characteristics of and findings for the 7 children with human T cell lymphotropic virus type 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP).

Patient	Age at IDH onset, years	Age at HAM/TSP onset, years	Time from onset to diagnosis of HAM/TSP, years	OMDS at first visit	OMDS at last follow-up visit	Progression rate[a]	CSF cell count, cells/mm^3	Form of HAM/TSP
I	2	5	5	3	5	1	9	Chronic
II	2	9	7	4	5	0.7	5	Chronic
III	1.4	9	2	1	3	1.5	35	Acute
IV	1.5	9	3	1	3	1	46	Subacute
V	5	11	0.5	0	1	2	40	Acute
VI	2	10	3	1	2	0.66	…[b]	Subacute
VII[c]	…	7	0.25	0	0	0	…[b]	Acute

NOTE. IDH, infective dermatitis associated with HTLV-1; OMDS, Osame's Motor Disability Score.

[a] The progression rate is the disability score divided by the time from onset to diagnosis, in years.

[b] Did not undergo CSF examination.

[c] The sibling without IDH.

The duration of HAM/TSP was defined as the time from onset to diagnosis. The interval between the diagnosis of IDH and of HAM/TSP was also recorded. The neurological diagnosis was based on clinical features and laboratory findings and was made in accordance with the diagnostic guidelines for HAM/TSP established by the World Health Organization [17, 18]. HAM/TSP cases were classified as definite or probable disease in accordance with Osame et al. [19].

Motor dysfunction was evaluated using Osame's Motor Disability Score (OMDS) [20] and the Expanded Disability Status Score (EDSS) [21]. Evaluation of the different systems was performed using the Functional System Score (FSS) [22]. The phase of disease was classified as acute, subacute, or chronic [10]. The progression rate of HAM/TSP was calculated by dividing the disability score by the duration of the disease in years [10, 17].

Laboratory investigation. For those patients who were suspected to have HAM/TSP, the following laboratory tests were performed: urine culture, parasitological stool examination, complete blood cell count, and measurement of serum levels of IgA, IgE, IgG, IgM, calcium, phosphorus, albumin, glutamic-oxalacetic/pyruvic transaminases, and alkaline phosphatase.

CSF. For CSF specimens, we measured cell counts and total protein and immunoglobulin levels. We also performed microorganism cultures and serological analysis for the infectious agents of HTLV-1, toxoplasmosis, cysticercosis, syphilis, and schistosomiasis. The classification of the cellularity levels was performed in accordance with criteria described elsewhere [23].

Anti–HTLV-1 antibody levels. Serum levels of HTLV-1 antibodies were measured by the ELISA test (Murex Biotech) with the end point dilution method.

Other examinations. MRI of the brain and spinal cord was performed and evaluated independently by 2 neurora-diologists. Chest x-ray and abdominal ultrasonography were also performed, and patients complaining of abdominal pain underwent gastric endoscopy.

Follow-up. The study population was followed-up at 2-month intervals. At each visit, a neurological evaluation was performed that included measurement of OMDS and EDSS, and laboratory findings were obtained from the complete blood cell count, stool examination, and urinary analysis.

RESULTS

HAM/TSP was diagnosed in 9 individuals: 6 patients with IDH (30%), 2 mothers (12.5%), and 1 sibling who did not have IDH. In 1 index case, a CSF sample was not obtained because the patient did not agree to the procedure.

Patients with HAM/TSP-Associated IDH

Epidemiological, clinical, and familial features. All 6 of the patients lived in Salvador. Five were female, and 1 was male. All of them were born after a normal pregnancy and delivery, with normal psychomotor development and no history of trauma. They were breast-fed, and the of breast-feeding ranged from 0.7 to 4 years (median, 2.4 years). None of the patients had received a blood transfusion, had had sexual activity before the diagnosis of HTLV-1 infection, or had experienced child abuse. The median age at onset of IDH symptoms was 2 years, and the median age at onset of HAM/TSP symptoms was 9 years. The median of HAM/TSP was 3.5 years. The time between the onset of IDH and the onset of HAM/TSP ranged from 3 to 8 years (median, 7.3 years) (table 2). The 6 patients with HAM/TSP associated with IDH came from 5 families that were not closely related. All mothers were seropositive, and 2 had HAM/TSP. Two pairs of case patients were siblings. Five other siblings were seropositive: 2 had IDH, 1 had HAM/TSP

Table 3. Neurological findings for the 6 patients with human T cell lymphotropic virus type 1 (HTLV-1)–associated infective dermatitis and HTLV-1–associated myelopathy/tropical spastic paraparesis, October 2002 to November 2004.

Neurological characteristic	At first visit	At last follow-up visit
Lumbago	6	6
Lumbago radiating to legs	3	6
Increase in urinary frequency	4	…
Urinary urgency	5	2
Urinary incontinence	2	…
Urinary tract infection	5	…
Abdominal pain	3	5
Weakness in lower limbs	3	5
Constipation	4	5
Deceased vibratory sensation	1	2
Hyperesthesia	2	3
Hoffman signs	3	3
Babinski reflex	3	6
Hyperreflexia of lower limbs	4	6
Hyperreflexia of upper limbs	1	2
Ankle clonus	3	6
Spasticity	3	4
Normal gait but unable to run	3	2
Gait disturbance	3	4

NOTE. Data are no. of patients.

without IDH, and 2 were HTLV-1 carriers. In 3 families, >1 case of HAM/TSP was observed: 3 cases in the first family (the mother and 2 children), 2 cases in the second family (the mother and 1 child), and 2 cases (siblings) in the third family.

General clinical and neurological examinations. Six patients had learning delay. Of these, 5 had short stature (2.5th percentile) and short fingers. In the 2 pairs of siblings with HAM/TSP, the onset of neurological manifestations occurred during a relapse of IDH. Other abnormalities observed were uveitis with cornea damage in 1 patient and mild mucosa pallor in all patients.

The main clinical findings are listed in table 3. The initial complaints were lumbago and pain in lower limbs, with difficulty in running. Two patients presented with typical HAM/TSP clinical manifestations at first visit (pyramidal signs, reduction in the vibratory sensations of both lower limbs, difficulty in walking uphill and in running, abnormal gait, and an OMDS of 3). At first examination, the other 4 patients presented an OMDS between 0 and 1. Three patients complained frequently of abdominal pain of unknown origin, which continued even after treatment for intestinal parasitism. In these cases, other pathologies were excluded by abdominal ultrasonography and endoscopy. Recurrent urinary tract infections and urinary disturbances were found in 5 patients with HAM/TSP. In 3 patients, urinary disorders (urinary urgency or incontinence) preceded the other neurological complaints. One patient had severe bladder disturbance, constipation, and persistent stool incontinence.

Laboratory examinations. The findings of laboratory examinations were normal except for the presence of mild hypochromic and microcytic anemia in all patients (table 1). An increase in serum IgE levels was also observed. Stool examination revealed *Ascaris lumbricoides* isolates in all cases, *Giardia lamblia* and *Strongyloides stercoralis* isolates in 2 cases, and an *Entamoeba histolytica* isolate in 1 case. *Schistosoma mansoni* isolates were not found in any patient.

Anti–HTLV-1 antibody titers. The serum antibody titers of the patients varied from 1:3.125 to 1:78.125 (table 1).

CSF examinations. The 5 patients with IDH who had CSF samples evaluated tested positive for HTLV-1 and negative for syphilis, toxoplasmosis, cysticercosis, and schistosomiasis. A mild increase in cellularity was detected, and cell counts varied from 5 to 46 cells/mm^3 (table 2). No atypical cells were found. A mild increase in total gammaglobulin level was observed, and direct examination and culture showed no microorganisms.

Other examinations. Findings of MRI of the brain and spinal cord were normal. Findings of ultrasonography and gastric endoscopy, performed in the 3 patients with complaints of abdominal pain, were normal.

Follow-up. Two cases of HAM/TSP were classified as acute and had durations (i.e., time from onset to diagnosis) of 0.5 and 2 years; 2 subacute cases had a duration of 3 years, and 2 chronic cases had durations of 5 and 7 years. The CSF cell counts were <10 cells/mm^3 for chronic cases and were >35 cells/mm^3 for the acute and subacute cases. One case of subacute disease was classified only on the basis of time from onset to diagnosis, because the patient did not agree to a CSF evaluation. In 3 patients, the OMDS increased by 2 points over a period of 2 years, and in 2 patients, the score increased by 1 point. In another recently diagnosed case (patient VI in table 2), motor capacity deteriorated quickly, with a 1 degree decrease in the OMDS in only 6 months. The analysis of functional systems, determined by the FSS, showed abnormalities in the sensory, pyramidal, and autonomic functional systems, and the EDSS varied from 1 to 6. The progression rate varied from 0.66 to 2 (table 2).

Treatment was given in accordance with the form of the disease and its rate of progression. Three cases were treated with intravenous administration of methylprednisolone for 3 days, followed by oral administration of prednisolone for 3 months. In 2 of these cases, there was poor motor response to treatment, but a substantial improvement in vesical status was observed. In the third case, in which there was severe vesical and intestinal dysfunction, the only improvement seen was some alleviation of urinary and fecal incontinence. Two patients

received oral prednisone therapy (2 mg/kg every other day for 5 days, followed by 1 mg/kg/day for an additional 2 months), with a favorable response.

Data for the Family Members

The 2 mothers received the diagnosis of HAM/TSP at 38 and 42 years of age. The CSF samples of both mothers tested positive for HTLV-1 and were negative for the infectious agents of HIV infection, toxoplasmosis, cysticercosis, syphilis, and schistosomiasis. The women were in the chronic phase of disease and had had symptoms of myelopathy for the past 8 years. Both had symptoms of HAM/TSP before giving birth to their children, and both breast-fed their children. One of them had received blood transfusions. Both had an OMDS and EDSS of 4. One of the mothers, who had a child with HAM/TSP, had an antibody titer of 1:78.125, and the other mother, who had 2 children with myelopathy, had an antibody titer of 1:625.

The 1 sibling (patient VII in table 2), a 7-year-old boy, had no skin disease and had received the diagnosis of HAM/TSP very recently. He had been breast-fed for 3 months, had no history of blood transfusion, and had no complaints. He was followed-up as an HTLV-1 carrier for 20 months, and in another, very recent neurological examination, asymmetric hyperreflexia and ankle clonus were detected. His OMDS and EDSS were equal to 0. His serum anti–HTLV-1 antibody titer was 1:625 when he was an asymptomatic carrier and was 1:1296 at the last follow-up visit. He had not yet undergone CSF examination, because he presented with varicella and cellulitis by *S. aureus*.

DISCUSSION

The diagnosis of HAM/TSP is based on clinical and laboratory data and usually requires exclusion of other causes of myelopathy, as well as demonstration of HTLV-1 infection [24]. In the present study, 6 cases of HAM/TSP were found among 20 cases of IDH, indicating a very high frequency (30%). According to the criteria given in the literature [19], 5 cases were considered to be definite HAM/TSP and 1 to be probable HAM/TSP, because there was no CSF finding available (the patient did not agree to the procedure). There are only 6 cases of the association of HAM/TSP with IDH previously reported in the literature [13–15]. Among the 9 siblings without IDH, we found 1 with probable HAM/TSP.

The predominance of female patients in this study was expected because both IDH and HAM/TSP are more prevalent in females [25, 26]. The infection was acquired vertically in all children, probably as a result of prolonged breast-feeding; in this study, the median duration of breast-feeding was 2.4 years. It has already been established that the frequency of vertical transmission is directly proportional to the duration of breast-feeding [27]. However, HAM/TSP also occurs in adults, mainly as a result of infection acquired through blood transfusion [10, 19].

According to the literature, HAM/TSP has 3 clinical phases: acute, subacute, and chronic [10]. On the basis of the time from onset to diagnosis and CSF cellularity, the 5 definite HAM/TSP cases were categorized as acute phase (2 cases), subacute phase (1 case), or chronic phase (2 cases). In addition, the sixth case, considered to be probable HAM/TSP, showed all the clinical manifestations of HAM/TSP and, as determined by the time from onset to diagnosis, was in the subacute phase. The sibling without IDH had HAM/TSP in the acute phase and had developed myelopathy very recently (table 2). Because this child did not undergo CSF evaluation, the patient was considered to have probable HAM/TSP [19].

HAM/TSP in adults generally begins after 40 years of age and evolves slowly. In this study population, a rapid progression of the disease was seen over a period of 2 years, with a considerable reduction in motor capacity and an increase in autonomic dysfunction, mainly in the patients with acute-phase HAM/TSP. Rapid progression has been described in adults aged >60 years who underwent blood transfusion [10, 14]. It is possible that this pathology has a rapid progression in its acute phase, followed by a slower progression from the fifth year of the disease onward. Clinical follow-up of the childhood and adolescent cases of HTLV-1 infection in which HAM/TSP was in the acute phase could contribute to an improved understanding of the evolution and progression of this disease.

Unlike HAM/TSP in adults, in the child and adolescent population of this study, no alterations were observed in MRI of the brain and spinal cord. The same has been described for the childhood and adolescent cases reported in the literature [14, 28]. As observed in this study, patients with HAM/TSP may present with autonomic dysfunction (vesical dysfunction and constipation) during the evolution of the disease [29, 30]. Persistent infection of the urinary tract was a frequent complication in 3 patients with urinary dysfunction. These infections may be caused by vesical dysfunction or by bacterial infection caused by skin lesions in the inguinal and genital regions or may be a consequence of the low socioeconomic and educational level of the patients and their family members.

Maloney et al. [31] observed severe anemia in HTLV-1–infected children, compared with noninfected children. In the present study, only a mild hypochromic and microcytic anemia was observed, certainly resulting from parasitic infections that were present in all patients. Short stature has been linked to HAM/TSP and IDH and is considered in these cases to be pseudohypoparathyroidism [32]. Uveitis with corneal damage has also been described in association with HTLV-1 infection [10].

Antibody levels were high in patients with both diseases, but much interpatient variation was observed. Considering that

there is a correlation between antibody titer and proviral load, it is probable that a high viral load is present in patients with both diseases, as previously observed by other authors [31, 33].

Clusters of HAM/TSP were observed in the present study in 3 families (i.e., there were 2 cases occurring simultaneously in the mother and child). In studies of HAM/TSP in juveniles, there are few reports of clustering [34–36]. The familial clustering of both diseases suggests a genetic background. The presence of some HLA haplotypes may have increased the children's susceptibility to HTLV-1 infection. Data reported by La Grenade et al. [35] suggest that the development of IDH may be linked to genetic factors. Those investigators studied 3 generations of the same family in which there were 9 carriers of HTLV-1 and 2 members with IDH associated with HAM/TSP—a mother and her child. Genotyping for HLA showed that only the mother, the child with IDH and HAM/TSP, and another carrier child had a class II DRB1*DQB1* haplotype [35]. In Japan, an immunogenetic background different from adult T cell leukemia/lymphoma has been observed in patients with HAM/TSP. In these patients, a high immune response to HTLV-1 was found [37].

Screening must be performed for all children and adolescents with myelopathy, as well as for all members of their family, not only to determine the presence of HAM/TSP but also to provide socially oriented education. These measures will prevent further dissemination of the HTLV-1 virus.

Acknowledgments

We are indebted to Professors Orlando Sales and Neide Ferraz, for their help.

Financial support. National Research Council (CNPq).

Potential conflicts of interest. All authors: no conflicts.

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