Juvenile Human T Lymphotropic Virus Type 1–Associated Myelopathy

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We report the cases of 5 adolescents with human T lymphotropic virus type 1–associated myelopathy/tropical spastic paraparesis, acquired in all but 1 case from the mother. The first symptom in all patients was difficulty in running, which was present for many years before the final diagnosis was made. Follow-up showed an indolent progression, regardless of treatment strategy.

Human T lymphotropic virus type 1 (HTLV-1) is the causative agent of HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), among other diseases [1, 2]. HAM/TSP is a chronic myelopathy typically characterized by a slowly progressive spastic paraparesis, severe sphincter disturbances, and slight objective sensory involvement. Although signs and symptoms manifest in most patients during adulthood, 10%–30% have onset before adulthood [3, 4].

The estimated number of people infected with HTLV-1 worldwide is 10–20 million [5]. The risk for development of HAM/TSP among individuals carrying HTLV-1 varies, but even if the lower end of the range, 0.25% [6], were used to estimate the number of affected individuals, 37,500 individuals (3750 cases of juvenile onset) would have the disease. Nevertheless, there have been only a few isolated reports of juvenile-onset cases [4, 7–10]. From 1989 through 2000, we have diagnosed HAM/TSP in 5 adolescents; clinical features and response to treatment are here described.

Methods. This is a descriptive study of patients in whom

HAM/TSP was diagnosed during 1989–2000 at the Institute of Pediatrics, Federal University of Rio de Janeiro, according to the diagnostic guidelines of the World Health Organization [11]. Serum and CSF samples were tested for the presence of HTLV-1 antibodies by ELISA (Vironostika HTLV-1/2; Organon Teknika) and Western blotting (HTLV WB 2.4; Diagnostic Biotechnology). Other causes of progressive myelopathy (spinal cord compression, vitamin B_{12} deficiency, and hereditary, congenital, and other inflammatory and traumatic myelopathies) were excluded for all patients. All patients were born after a normal pregnancy and delivery and reached developmental milestones at normal ages; none had a history of consanguinity, familial cases of spastic paraparesis, or trauma. Laboratory tests, spinal imaging, and CSF analysis excluded other causes. The Institutional Review Board of the Federal University of Rio de Janeiro approved this study, and informed consent was obtained from patients or their parents.

Case reports. Epidemiological and clinical features are summarized in table 1. The main results of diagnostic studies are shown in table 2.

Patient 1, a girl who was breast-fed for an unknown period of time and whose mother was infected with HTLV-1, received a diagnosis of HAM/TSP at the age of 11 years. Since the patient was 6 years old, she had been unable to run as well as others of the same age and complained of pain in the back and legs, which was thought to be due to arthralgia. Because of progressive difficulty in walking and urinary urgency, the patient was referred to a neurologist at age 11 years. She was able to walk only with support and had proximal weakness (Medical Research Council [MRC] scale score, 3/5), hypertonia, brisk tendon jerks, clonus, and Babinski signs in the lower limbs. Progressive deterioration occurred, despite medial treatment (with baclofen, vitamin C, imipramine, and steroids), and the patient became wheelchair-bound at age 20 years, with urinary incontinence and constipation. Recurrent urinary tract infections, ocular tuberculosis, and warts were seen during follow-up.

Patient 2 had never been able to run as well as her schoolmates, complained of leg pain, was found to have keratoconjunctivitis sicca, and was given a diagnosis of Sjögren syndrome by a rheumatologist (results of testing of a lip biopsy specimen were negative). The patient also had thyroiditis, growth hormone deficiency, abnormal renal function, and hemolytic anemia. She was referred to a neurologist at the age of 12 years. At that time, the patient had infective dermatitis, short stature (height, 120 cm; z score, -4.06), inability to walk without

Table 1. Epidemiological and clinical features of human T lymphotropic virus type 1–associated myelopathy/tropical spastic paraparesis in 5 juvenile patients in Brazil.

Characteristic	Value
Female sex	5
Mother-to-child transmission	4
Age at onset of first neurological symptoms, median years (range)	7 (6–12)
Age at diagnosis, median years (range)	12 (11–17)
White skin color	3
Infective dermatitis	4
Short stature	3
Urinary tract infections	2
Ophthalmologic features	
Tuberculosis uveitis	1
Keratoconjunctivitis sicca	1
Corneal infiltrate	1
Endocrine disorders	1
Nephropathy	1
Neurological features	
Progressive paraparesis	5
Symptoms of lower leg weakness	5
Pain (back or lower limb)	4
Urinary urgency or incontinence	4
Pyramidal signs	2
Sensory signs	2
Cerebellar signs	1
Distal limb atrophy	1

NOTE. Data are no. of patients, unless otherwise indicated.

support, proximal limb weakness (MRC scale score, 4/5), diffuse brisk tendon jerks, hypertonia, and clonus in the lower limbs. The patient had not been breast-fed, but she had a history of transfusions to treat anemia, and one of the blood donors had positive results of tests for HTLV-1 done after the transfusion had occurred. She was treated with steroids, cyclophosphamide, and methotrexate but had rapidly progressive disease and died from renal failure at the age of 15 years.

Patient 3, a girl who had been breast-fed until age 3 years and whose mother was infected with HTLV-1, had a history of difficulty in running since the age of 7 years, difficulty in climbing steps since the age of 9 years, and complaints of pain in her back and legs. She had received a diagnosis of arthralgia. Recurrent urinary tract infections, urinary urgency, and infective dermatitis were also present. When the patient was 11 years old, neurological examination demonstrated proximal weakness (MRC scale score, 4/5), hypertonia with brisk tendon jerks, Babinski signs, and diminished distal vibration sense; all signs were present predominantly in the lower limbs. The patient was able to walk unassisted, although for a shorter distance than was usual for a child her age. After 2 years, despite medical

treatment (with steroids, vitamin C, pentoxifylline, imipramine, and baclofen), she occasionally needed to use a walking aid.

Patient 4 had a history of difficulty in running from the age of 12, progressing to difficulty in climbing stairs and urinary urgency. She had been breast-fed until the age of 2 years. At 14 years of age, the patient had short stature (height, 143 cm; z score, −2.63) and infective dermatitis; she was unable to walk without assistance and had generalized weakness, brisk tendon jerks, hypertonia, Babinski signs, ataxia, nystagmus, and optic atrophy. After treatment with steroids, vitamin C, oxybutynin, and amitriptyline, the patient regained the ability to climb stairs and no longer had urinary urgency. Her father also presented with a myelopathy, which had started 2 years after he received radio- and chemotherapy for a neck adenocarcinoma. He was tested and found to be HTLV-1 positive, as were all other immediate family members (including the patient's mother, brother, and sister).

Patient 5 had experienced difficulty in running, with pain in her legs, from the age of 9 years. She received a diagnosis of idiopathic osteoporosis and had short stature (height at the age of 12 years, 134 cm; z score, −2.25). The patient was referred for neurological evaluation at the age of 17 years because of progressive difficulty in walking and urinary urgency. She was able to walk unassisted for a short distance only, with distal atrophy of all limbs, lower limb weakness (MRC scale score, 3/5), generalized brisk tendon jerks, clonus, Babinski and Hoffmann signs, diminished distal vibration sense, and corneal infiltrates. Electroneuromyography showed low motor fibular amplitude, fibrillations, and rarefaction. The patient also had a history of skin lesions that had the characteristics of infective dermatitis. She had been breast-fed until the age of 1 year, and her mother was found to be infected with HTLV-1. Treatment was started (with vitamin C, baclofen, and pentoxifylline), and at the age of 18 years, she still needs occasional help in walking and receives treatment.

Discussion. HAM/TSP may be found in children. The first report of a juvenile patient was made in 1987 [9, 10]: a 13-year-old black boy had occasional cramps, persistent clonus, and Babinski sign in the right lower extremity. The patient's parents had classic HAM/TSP. The 2 youngest patients in our series were 11 years old at diagnosis, an age similar to that of the patients whose cases were reported by Kayembe et al. [4]. However, difficulty in running and pain in the legs or back were found to have been present since childhood in most of our patients. This difficulty manifested, many years before a neurological evaluation was made, as inability to run as fast as children of the same age or as pain in the legs during running and progressed to a total inability to run. Bhigjee et al. [12] described a possible case of infantile onset. However, the diagnosis was not confirmed by a finding of antibodies in CSF, and the presence of developmental delay with poor fetal move-

Table 2. Results of diagnostic studies of 5 juvenile patients in Brazil with human T lymphotropic virus type 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis.

Diagnostic test	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ELISA/Western blotting for HTLV-1 antibodies in serum and CSF	Positive	Positive	Positive	Positive	Positive
Spinal imaging					
Myelographic examination	No abnormalities	No abnormalities	No abnormalities	No abnormalities	—
MRI	—	—	—	—	No abnormalities
CSF analysis					
Protein level, mg/dL	23	16	25	34	18
Mononuclear cell count, no.	6	5	4	1	5
Serologic analysis					
Vitamin B_{12} level, ng/mL	300	220	630	470	540
Calcium level, mg/dL	9.4	9.3	9.1	10.3	10
Phosphorus level, mg/dL	4	4.5	4.3	4.5	4.2

ments could suggest another cause for the spastic paraparesis that was found in that patient at the age of 3 years.

We saw only female adolescent patients with HAM/TSP. The disease may be found in male adolescents as well [9, 10], but the predominance in female adolescents, as seen in other juvenile reports [3, 7, 8], is consistent with the general diagnostic guidelines [11].

One of our patients acquired the infection from blood transfusion. Routine blood-donor screening for HTLV was started in Brazil in December 1994. HTLV-1 can be transmitted by sexual contact with an infected person, by sharing of contaminated needles and syringes between drug users, by transfusion of contaminated blood, and from mother to child. Transfusion is perhaps the most efficient mode of virus transmission; the probability of seroconversion in a recipient of contaminated blood is 40%–60%, and the median time to seroconversion is 51 days [13].

Mother-to-child transmission was the most frequent means of transmission among our patients, as would be expected among juvenile patients. Breast-feeding for >6 months has been associated with transmission, with a probability of mother-to-infant transmission of 18%–30%, but infection still occurs in ∼3% of children who are not breast-fed [14]. Some countries have, therefore, proposed antenatal HTLV screening with recommendation of formula feeding [14].

Our patients had no clinical features that were strikingly different from those of patients described by others. Cerebellar signs and atrophy have been described [4, 7]. The same is true for previous reports on infective dermatitis evolving to HAM/TSP [8] and for reports on arthropathy or collagen vascular diseases associated with HAM/TSP [15–17]. Indeed, infective dermatitis, which was present in 4 of our patients, seems to be a childhood disease that is commonly seen in association with HTLV-1 [18–20].

Three of our patients had short stature without other features of parathyroid dysfunction. Pseudohypoparathyroidism (i.e., resistance to parathyroid hormone) results in hypocalcemia, retention of phosphate, and bone demineralization. This has been shown to occur in Japanese patients with HAM/TSP who present with short stature and hypocalcemia as adults, most of whom had juvenile onset of HAM/TSP [3]. One of our patients had nephropathy; another had a uveitis due to tuberculosis. HTLV-1–associated uveitis, adult T cell leukemia/lymphoma, mycosis fungoides, and nephropathy have been reported in children and adolescents [21–26].

The disease had a relentless progressive course in our patients. Because only mild symptoms often are seen for many years, the disease usually remains undiagnosed until major walking disabilities develop. Only the patient who acquired the infection from blood transfusion experienced a rapid progression that resulted in death from renal failure 2 years after the diagnosis of HTLV-1 disease. This finding is consistent with reports made by Osame et al. [27]. Conflicting evidence with regard to the rate of progression in patients who are younger at onset indicates that prospective studies of HAM/TSP are warranted, to improve understanding of the natural history of the disease [27, 28].

Foci of HTLV-1 infection are found in distinct geographic clusters and affect several million persons worldwide. The infection is endemic in southern Japan, the Caribbean, sub-Saharan Africa, the Middle East, South America, the Pacific Melanesian islands, and Papua New Guinea. Brazil, the largest South American country both in area and in population, has a median seroprevalence of HTLV-1 among blood donors of ∼0.45% [29]. Taking together this seroprevalence rate, the risk rate for development of HAM/TSP in HTLV-1 carriers [6], and the Brazilian population (according to the last census, 170 million), one would expect to find a total of 2000 patients with HAM/TSP in Brazil. If 10%–30% have onset before the age of 20 years, 200–600 of these cases would be pediatric cases.

A 5-year (mean) period elapsed from onset of symptoms to diagnosis in our series. This is an important finding, and, although it has been reported in several other series, it has not been dealt with properly. The reasons for the delay in the diagnosis should be sought regionally, because there may be different factors as a result of the different health systems that serve each country. In our case, the period of referral for neurological evaluation was too long, particularly for patients who complained of leg pain. Pediatricians sought help from an orthopedist or rheumatologist for patients who had difficulty in walking before referring these patients to a neurologist. It is important, therefore, that all of those involved in the care of children in regions in which HTLV-1 is endemic become acquainted with the possible disorders related to this virus and include HTLV-1 infection in the differential diagnosis. Suspicion of such a diagnosis in children should prompt earlier diagnosis and treatment, which might result in better outcomes.

Acknowledgment

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