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Short Communication

Subacute progression of human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis

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Although human T-lymphotropic virus type I (HTLV-I)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) is usually described as a chronic disabling disease, a rapid course over months or even weeks has been reported in some patients. The authors describe the clinical features of HAM/TSP in a Brazilian cohort and evaluate the prevalence of patients with a subacute progression of the disease. This was defined as the requirement of a wheelchair during the first 2 years after the onset of symptoms. Patients with this subacute course and patients with the chronic clinical course were compared in terms of their HTLV-I proviral loads (PLs) using real-time polymerase chain reaction (PCR). Seven out of 88 patients (7.9%) had a subacute progression. All patients were women and 5/7 acquired HTLV-I through sexual contact. There was no significant difference in the real-time PLs between the group with subacute evolution (mean 8.5 copies/100 cells, range 6.03 to 12.09) and those patients with a typical course of disease (mean 11.34 copies/100 cells, range 0.4 to 67.72) ($P = .68$), suggesting that factors other than the number of infected cells are implicated in the development of such an aggressive course of disease. Early recognition of this subgroup is important because immunosuppressive treatment might be beneficial if instituted promptly. *Journal of NeuroVirology* (2007) **13,** 468–473.

Keywords: disease progression; human T-lymphotropic virus 1; myelopathy; proviral load

Introduction

Human T-lymphotropic virus type I (HTLV-I)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic disabling disease caused by the HTLV-I. It is estimated that 10 to 20 million people are infected with HTLV-I worldwide (de The and Bomford, 1993); however, only 2% of the infected individuals will develop neurological disease (Maloney *et al*, 1998). HAM/TSP has been reported in HTLV-I endemic areas such as the Caribbean, southern Japan, equatorial Africa, Middle East, South America, and Melanesia (Madeleine *et al*, 1993). The disease affects mainly the lateral columns of the spinal cord at the thoracic level. Anterior and posterior columns are affected in a lesser extension (Jacobson, 2002). Lesions are associated with perivascular and parenchymal lymphocytic infiltration and the presence of macrophages, proliferation of astrocytes, and fibrillary gliosis (Iwasaki, 1990). Clinical features include spastic paraparesis, hyperreflexia, urinary incontinence, impotence, constipation, sensory disturbances, and low back pain (Manns *et al*, 1999).

The disease onset in the majority of the affected individuals is insidious and the progression is usually slow over the years. Forty-five percent of all patients

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cannot walk unassisted and 30% are bedridden after 10 years of diagnosis (Gessain and Gout, 1992). Nonetheless, subacute evolution of HAM/TSP over months or even weeks has been reported (Carod-Artal and Vazquez-Cabrera, 2000; Kida *et al*, 1997; Shakudo *et al*, 1999; Watanabe *et al*, 2001). The factors associated with such aggressive course are unknown, but these patients with a subacute evolution of the neurological deficits may represent a subgroup in which aggressive immunosuppressive treatment may halt the progression of the myelopathy and prevent further disability.

The present study aimed to evaluate the prevalence of patients with a subacute progression of HAM/TSP and to compare the HTLV-I proviral load (PL) between this group and patients with the more typical chronic course of the disease.

Results

Fifty-five patients (31%) were excluded from the analysis because of the coexistence of other diseases that potentially could interfere with the clinical progression. Thirty-two eligible patients (18%) missed the clinical visits during the study period and were also excluded. The clinical and demographic features of the remaining 88 patients are described in Table 1. The mean age of the study group was 53.1 years (range 23 to 75 years) and 68.2% were women. The mean age at onset was 40.7 years (range 12 to 67 years) and the mean length of disease was 12.5 years (range 2 to 40 years). The median Instituto de Pesquisa Clínica Evandro Chagas (IPEC) disability scale among the 88 patients was 15 (range 3 to 26).

Table 1 Clinical and demographic features

	N	%
Type of onset		
Motor	64	73
Sensory	4	5
Sphincter	10	11
Low back pain	10	11
Handicap		
Walk without help	13	14.8
Walk with support	37	42
Confined to a wheel chair	38	43.2
Probable source of infection		
Blood transfusion	13	14
Vertical transmission	12	15
Intravenous drug use	3	3
Sexual contact	60	68
History of sexual transmissible disease	21	23.9
History of tuberculosis	10	11.4
Asymmetric symptoms	73	83
Low back pain	55	62.5
Current steroid use	6	6.8
Late onset of disease (≥50 years)	22	25
Pyramidal syndrome in lower limbs	88	100
Increased tendon jerks in upper limbs	25	28.4
Sensory deficits	46	52.3
Increased jaw reflexes	4	4.5
Postural tremor	15	17
Decreased ankle jerks	21	23.9

Thirty-eight patients needed wheelchair assistance. The mean time from onset of symptoms to wheelchair was 10.4 years (range 0.1 to 37 years). Seven patients (7.9%) were classified as subacute progressors. All of these patients were women and the mean age at onset was 49.5 years. Sexual contact was the probable source of infection in 5/7 patients. The mean time from onset to wheelchair in this subgroup was 8.5 months (range 1 to 23 months). Clinical features of these patients are summarized in Table 2. A thoracic spinal cord magnetic resonance imaging (MRI) was performed in 3/7 patients with subacute disease. In two, the examination was considered normal, but in one, there was a discrete hyperintense lesion in T2-weighted lesion associated with edema of the spinal cord. Four out of seven underwent electromyography. In two, there was evidence of motor neuron disease and in two, no abnormalities were observed.

HTLV-I PL was determined in all patients with subacute evolution and in 68 individuals with chronic course of HAM/TSP. There was no significant difference in the HTLV-I PL between the group with a faster progression (mean 8.5 copies/100 cells, range 6.03 to 12.09) and the other participants (mean 11.34 copies/100 cells, range 0.4 to 67.72) ($P = .68$) (Figure 1).

Discussion

In the present study, we analyzed the disability status in a Brazilian HAM/TSP population free of other serious systemic or neurological diseases that could interfere with the progression of this condition. Even with more strict exclusion criteria, the epidemiological and clinical features of our

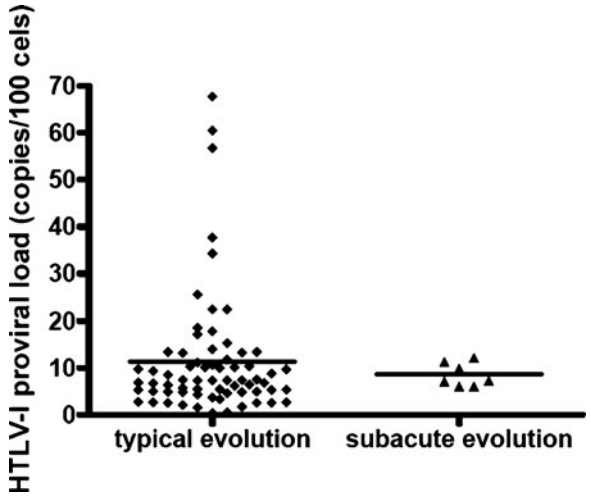

Figure 1 HTLV-I proviral load in patients with subacute evolution and typical course of HAM/TSP. Lines represents means.

Table 2 Clinical and virological features of patients with subacute progression

Patients	*Age at onset*	*Probable source of infection*	*First symptom*	*Other HTLV-I–related manifestations*	*Progression to wheelchair (months)*	*HTLV-I proviral load (copies/100 cells)*
1	37	Blood transfusion	Leg weakness	Postural tremor, hypothyroidism, xerosis	1	9.84
2	23	Vertical	Leg weakness	Postural tremor, xerosis	1	7.28
3	43	Sexual contact	Leg weakness	Xerosis, xerophthalmus, peripheral neuropathy, hypothyroidism adult T-cell leukemia	3	11.3
4	65	Sexual contact	Leg weakness	Xerosis	8	12.9
5	56	Sexual contact	Arthralgia	Xerosis	12	7.08
6	59	Sexual contact	Leg weakness	Peripheral neuropathy	12	6.03
7	64	Sexual contact	Lumbar pain	Peripheral neuropathy, xerophthalmus	23	6.04

population were similar of those described in previous studies (Araujo *et al*, 1998; Nakagawa *et al*, 1995), except for a high prevalence of patients with absent ankle jerks. In the lack of other predisposing factors, this finding could be explained by the coexistence of a peripheral neuropathy secondary to HTLV-I (Leite *et al*, 2004). Peripheral nerve involvement has been described in HAM/TSP patients, but its pathogenesis is presently unknown (Kiwaki *et al*, 2003).

The prevalence of subacute forms of HAM/TSP is 4.7% to 21.5% in different series (Castillo, 1989; Cruickshank *et al*, 1989; Gotuzzo *et al*, 2004; Nakagawa *et al*, 1995; Roman *et al*, 1987). However, there is no standard definition of subacute progression in HAM/TSP and different criteria have been used. According to Nakagawa *et al,* subacute progression was defined as deterioration in more than three grades on the motor disability grading for HAM/TSP over 2 years (Nakagawa *et al*, 1995). Recently, Gotuzzo *et al* described rapid progression in 21.5% of Peruvian HAM/TSP patients using as definition the inability to walk unaided within the first 2 years from symptoms onset (Gotuzzo *et al*, 2004). The lower prevalence found in our study (7.9%) reflects the more stringent criteria employed and the exclusion of patients with other diseases that could potentially have modified the clinical evolution. Our criteria seem to be more practical and reliable for the definition of subacute progression because they are representative of the severity of the clinical status in the affected patients and can be easily assessed, avoiding an interpretation bias and the use of clinical scales that are not promptly available everywhere.

In this study, all patients were women and most of them had acquired HTLV-I thorough sexual contact. Several factors have been associated with a faster clinical progression in HAM/TSP patients such as blood transfusion as the source of infection (Gout *et al*, 1990) and increased titers of neopterin and HTLV-I antibodies in the cerebrospinal fluid (CSF) (Nakagawa *et al*, 1995). The role of age at onset in the clinical progression is controversial, because both early (Kuroda *et al*, 1991a) and late (Gotuzzo *et al*, 2004; Olindo *et al*, 2006) onset of disease have been associated with a faster evolution of the symptoms. The influence of the gender has been also a matter of debate. Previously, we have shown that in a group of Brazilian HAM/TSP patients, women had a worse clinical progression than men (Lima *et al*, 2005). However, in a recent prospective study in Martinique, gender had no apparent effect in the progression of the motor symptoms (Olindo *et al*, 2006).

It is known that the HTLV-I PL is higher in HAM/TSP than in asymptomatic carriers (Nagai *et al*, 1998) and a high PL usually predates the development of neurological symptoms (Taylor *et al*, 1999). More recently, it has been shown that the HTLV-I PL parallels the course of HAM/TSP, being higher in patients with a faster progression of the symptoms (Matsuzaki *et al*, 2001; Olindo *et al*, 2005, 2006). Interestingly, in our study, there was no significant difference between the HTLV-I PL of patients with subacute evolution and those with a more typical course of disease. One can argue that HTLV-I PL was determined years after the onset of the symptoms and the number of infected cells could have decreased over the time, but Kwaan *et al* have demonstrated that PL was stable over 10 years in a group of HTLV-I–infected individuals (Kwaan *et al*, 2006). These data suggest that factors other than a high proviral load are implicated in the development of subacute HAM/TSP. The pathogenesis of the disease has not been completely understood, but there is increasingly evidence of the important role of the inflammatory reaction mediated by CD8+ lymphocytes, which are a key component of the immune response against different viruses. First, a higher frequency of HTLV-I-specific cytotoxic T lymphocytes (CTLs) has been demonstrated in the blood and cerebrospinal fluid of HAM/TSP when compared to asymptomatic carriers (Kubota *et al*, 2000). Second, infiltrating CD8+ cells have been found in the inflammatory lesions of the spinal cord. These HTLV-I–specific CTLs could recognize productively infected cells and respond either by direct killing or through the release of proinflammatory cytokines. Both processes could

lead to secondary damage to the central nervous system tissue and the development of the myelopathy (Araujo and Silva, 2006). Based on these data, we could speculate that a stronger inflammatory reaction in some patients could lead to a subacute deterioration of the clinical status. Further support to this idea is given by a recent report of the presence of spinal cord edema and contrast enhancing lesions at the spinal cord MRI of a patient with acute progressive HAM/TSP (Silva and Araujo, 2004).

To date, there is no specific treatment for HAM/TSP. However, different immunomodulatory or anti-inflammatory drugs such as methylprednisolone (Araujo *et al*, 1993), immunoglobulin (Kuroda *et al*, 1991b), interferon alpha (Nakamura *et al*, 1990), and danazol (Harrington *et al*, 1991) have been used. The success of these therapies may depend on the duration of the disease, because it has been shown that early in the illness, marked inflammation is present but this picture is gradually replaced by degeneration of the white matter and glio-mesenchymal tissue reactions later in the course of the disease (Iwasaki, 1990). Patients with subacute progression and additional evidence of an ongoing inflammatory central nervous system (CNS) process such as pleocytosis or spinal cord MRI showing contrast-enhancing lesions represents a subgroup in which, potentially, an early and aggressive immunosuppressive intervention would be more beneficial in order to halter an ominous evolution to spinal cord atrophy.

In conclusion, there is a small but significant group of patients with HAM/TSP and subacute evolution. HTLV-I PL in this group was similar to patients with a more chronic course of the disease. Prospective studies to determine the pathophysiologic mechanisms involved with the development of subacute forms of HAM/TSP and the efficacy of an early immunosuppressive treatment are therefore necessary.

Subjects and methods

Study design and patients
We reviewed the files of 175 HTLV-I–infected patients evaluated at the outpatient clinic of the Reference Centers for Neurological Infections and HTLV-I, Instituto de Pesquisa Clínica Evandro Chagas (IPEC), FIOCRUZ, Rio de Janeiro, Brazil. Patients were included in the study if they fulfilled the World Heath Organization's diagnostic guidelines for HAM/TSP (Osame, 1990). Patients were excluded if they had concurrent infections like HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus), syphilis, HTLV-II, or other disabling diseases that could interfere with the clinical progression (hepatic, renal or cardiac failure, diabetes mellitus, osteoarthritis, and other neurological diseases).

The eligible patients were enrolled between June 2002 and February 2003 and submitted to a clinical questionnaire and physical examination performed by an experienced neurologist. Clinical severity was evaluated through the IPEC disability scale, which was developed exclusively for the prospective assessment of HAM/TSP. This scale is a composite of motor, pain, sensory, and sphincter scores (Lima *et al*, 2005). To evaluate the percentage of patients with an unusual subacute progression of symptoms, we defined acute progression as the requirement of a wheel chair during the first 2 years after the onset of symptoms.

Real-time polymerase chain reaction
HTLV-1 PL in peripheral blood leukocytes was measured by real-time PCR assay (SmartCycle, Cepheid) using the TaqMan system (Applied BioSystem). Standard curves were generated by the amplification of a β-globin gene fragment from HTLV-I–negative genomic DNA and the HTLV-1 p*X* region (*tax* gene) fragment from a cell line containing a single copy of HTLV-1 provirus (TARL-2) (Tateno *et al*, 1984). PCR was performed using 200 ng of DNA with 12.5 μl of TaqMan 2× universal PCR master mix (Applied BioSystems), 15 pmol for p*X* primers, 50 pmol for β-globin primers, and 2.5 pmol of the fluorescent probes added to a total volume of 25 μl. The HTLV-I PL was calculated as: copies/100 cells = [*tax* copies (β-globin copies/2)] × 100. The lower limit of detection was 1 copy per 10^4 cells.

Statistical analysis
The Mann-Whitney *U* test was used to compare the HTLV-I proviral loads between patients with subacute evolution and the other participants. All *P* values were two sided and an $\alpha = .05$ was employed.

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