ORIGINAL ARTICLE

Neurological manifestations in individuals with HTLV-1-associated myelopathy/tropical spastic paraparesis in the Amazon

GAS Dias¹, GT Yoshikawa², RVL Koyama³, S Fujihara³, LCS Martins⁴, R Medeiros¹, JAS Quaresma³ and HT Fuzii¹

Study design: A cross-sectional observational study was conducted.

Objective: The aim was to analyze the clinical–functional profile of patients diagnosed with HTLV-1 (human T-lymphotropic virus type 1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in the Amazon region.

Setting: Reference center for HTLV in the city of Belém, state of Pará, Brazil.

Methods: Muscle strength, muscle tone, balance and the need for gait assistance among patients with HAM/TSP were evaluated.

Results: Among the 82 patients infected with HTLV-1, 27 (10 men and 17 women) were diagnosed with HAM/TSP. No statistically significant difference in muscle tone or strength was found between the lower limbs. Muscle weakness and spasticity were predominant in the proximal lower limbs. Patients with HAM/TSP are at a high risk of falls ($P=0.03$), and predominantly use either a cane or a crutch on one side as a gait-assistance device ($P=0.02$).

Conclusion: Patients with HAM/TSP exhibit a similar clinical pattern of muscle weakness and spasticity, with a high risk of falls, requiring gait-assistance devices.

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INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1) is associated with the chronic, persistent infection of T cells, which can result in neoplastic or inflammatory diseases, such as adult T-cell leukemia or lymphoma and HTLV-1-associated myelopathy (HAM), also known as tropical spastic paraparesis (TSP). However, HTLV-1 is associated with disease in only ~5% of infected individuals, as most remain asymptomatic.^{1,2}

HAM/TSP is characterized by the insidious onset of slowly progressive weakness and spasticity of one or both legs, together with hyperreflexia, ankle clonus, extensor plantar responses and low-back pain. Other features include detrusor instability leading to nocturia, urinary incontinence and minor sensory changes, especially paresthesia and the loss of sense of vibration.^{3–7}

Patients with HAM/TSP exhibit physical disabilities that require rehabilitation to minimize functional loss. Considering the need to establish the clinical characteristics related to motor function in such patients, the aim of the present study was to determine the clinical–functional profile of individuals with HAM/TSP.

MATERIALS AND METHODS

An observational, cross-sectional study was conducted to evaluate functional and neurological manifestations in patients with definite HAM/TSP. Patients with a diagnosis of HAM/TSP were selected from 82 HTLV-1-infected outpatients treated at the Epidemiological Clinic of Endemic Diseases of the Tropical Medicine Sector of the Federal University of Pará (Brazil). A total of

82 patients were diagnosed with HTLV-1, among which 27 met the criteria of the WHO (World Health Organization) as well as the criteria established by De Castro-Costa for HAM/TSP.⁸ The serological diagnosis of the infection was performed using enzyme-linked immunosorbent assays and confirmed by PCR. The clinical diagnosis of HAM/TSP was performed by a medical team, including a neurologist, a rheumatologist and an infectiologist.

The following inclusion criteria were established: 18 years of age or older, either gender, HTLV-1 antibodies in the serum and a positive PCR for HTLV-1 in the blood without co-infection by immunosuppressive viruses, and a diagnosis of HAM/TSP based on the criteria of the WHO. Individuals were excluded from the study if they had a positive PCR for HTLV-2 or disorders that can resemble HAM/TSP (differential diagnosis). The following conditions were excluded: multiple sclerosis; carcinomatous meningitis, familial spastic paraparesis, transverse myelitis, primary lateral sclerosis, paraneoplastic syndrome, syringomyelia, Lyme disease, B12 or folic acid deficiency, Behçet's disease, neurosyphilis, neurotuberculosis, sarcoidosis, HIV vacuolar myelopathy, collagen vascular disease, autoimmune myelopathy, Sjögren's syndrome, toxic myelopathy, amyotrophic lateral sclerosis, fungal myelopathy, spinal arteriovenous fistula, hepatic myelopathy, parasitic myelopathy (visceral larva migrans of *Toxocara canis* and *Ascaris suum*), spinal cord compression (spinal tumor, cervical spondylosis, brain parasagittal tumor and so on.) and endemic regional myelopathy with similar clinical manifestations (including schistosomiasis and neurocysticercosis).⁸

Patients with HAM/TSP were assessed with regard to muscle strength, muscle tone, balance and walking deficiency by physicians and a physiotherapist. For the assessment of muscle strength, the scale proposed by the Medical Research Council was employed, which uses a numeral grade ranging

¹Núcleo de Medicina Tropical, Universidade Federal do Pará, Belém, Brazil; ²Instituto de Ciências da Saúde, Universidade Federal do Pará, Belém, Brazil; ³Centro de Ciências Biológicas e da Saúde, Universidade do Estado do Pará, Belém, Brazil and ⁴Centro de Ciências Biológicas e da Saúde, Universidade da Amazônia, Belém, Brazil

Correspondence: Dr GAS Dias, Núcleo de Medicina Tropical, Universidade Federal do Pará, Avenida Generalíssimo Deodoro, Belém 66055-240, Brazil.

E-mail: georgealbertodias@yahoo.com.br

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from 0 to 5 points.⁹ The hip flexors were considered the proximal muscle group, and knee extensors and ankle plantar flexors were considered the distal muscle groups. All the patients were seated during the evaluation.

The Modified Ashworth Scale was used to analyze muscle tone,¹⁰ which involves manually moving a limb through its range of motion to passively stretch specific muscle groups. This scale measures passive resistance in the joint, as the examiner perceives it. The hip adductors, knee extensors and ankle plantar flexors were used as references for the general classification of the patients.¹¹

The evaluation of balance was performed using the Tinetti Performance-Oriented Mobility Assessment.¹² The maximum score on the scale is 28 points. Scores <19 indicate a greater risk of falls. A score between 19 and 24 points indicates a moderate risk, whereas scores 25–28 indicate low risk.

The degree of walking deficiency was characterized by the use of gait-assistance devices, which were classified progressively as follows: (0) no gait-assistance device; (1) help by third parties; (2) use of a walking stick/cane or crutch on one side; (3) use of bilateral crutches; (4) use of a walker; and (5) use of a wheelchair. As the patients had different gait-assistance devices, the predominant one was considered for the score.

Table 1 Functional neurological profile of patients with HAM/TSP

Variables	N (%)	Median	P-value
Sex			
Male	10 (37%)	—	0.24*
Female	17 (63%)		
Age			
Mean ± standard error	51.2 ± 9.86 years	—	—
Median	54 years		
Muscle strength (n = 27)			
Proximal right weakness	20 (80%)	4	0.76**
Proximal left weakness	21 (84%)		
Distal right weakness	15 (60%)	4	0.78**
Distal left weakness	15 (60%)		
Spasticity (n = 27)			
Right adductor	24 (89%)	1+	0.85**
Left adductor	23 (85%)		
Right quadriceps	23 (85%)	1+	0.93**
Left quadriceps	23 (85%)		
Right plantar flexor	20 (74%)	1+	0.97**
Left plantar flexor	21 (78%)		
Balance (n = 21)			
Low fall risk	2 (10%)	17	0.03***
Moderate fall risk	8 (38%)		
High fall risk	11 (52%)		
Degree of walking aid required (n = 27)			
No aid	8 (30%)	2	0.02***
Help from third parties	3 (11%)		
Walking stick or crutch on one side	9 (33%)		
Crutch on both sides	0 (0%)		
Walker	2 (7%)		
Wheelchair	5 (19%)		
Evaluation of balance walk unaided (n = 8)			
Low risk of falls	2 (25%)	22.5	0.07***
Moderate risk of falls	4 (50%)		
High risk of falls	2 (25%)		

* χ^2 -test, $P \leq 0.05$; **Mann-Whitney test, $P \leq 0.05$; ***G test (Adherence), $P \leq 0.05$.

Descriptive and inferential statistics were used to analyze the clinical features of the patients. Categorical variables were expressed as frequencies, as well as mean and s.d. values. The G test (adherence), Mann-Whitney test and χ^2 -test were employed to determine the significance of the data using a P -value of ≤ 0.05 as the threshold level. All statistical analyses were performed using the Epi Info version 3.5.2 (Atlanta, GA, USA) and GraphPad Prism 5.0 (La Jolla, CA, USA) programs.

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this study.

RESULTS

The sample comprised 27 patients with HAM/TSP (10 males (37%) and 17 females (63%), with no significant gender difference ($P = 0.24$)). The mean and median ages were 51.2 ± 9.86 and 54 years (range: 35–69 years), respectively, with no significant difference.

Three patients were excluded from analysis for not completing the evaluation. The analysis of lower limb muscle strength indicated that the patients with HAM/TSP exhibited muscle weakness (median value = 4). However, no significant differences were found in the strength of left and right legs or the proximal ($P = 0.76$) and distal muscles ($P = 0.78$). The majority of patients exhibited muscle weakness in the proximal lower limbs ($n = 21$; 84%). Some individuals also exhibited reduced muscle strength in the distal region ($n = 15$; 60%; Table 1).

In the evaluation of spasticity, a median score of 1+ was found for the three muscle groups tested (hip adductors, knee extensors and ankle plantar flexors), suggesting a slight increase in muscle tone. No significant differences were found between the right or left legs for any of the muscles evaluated: hip adductors ($P = 0.85$), knee extensors ($P = 0.93$) and ankle plantar flexors ($P = 0.97$).

Comparing the muscle groups most affected by spasticity, the majority of patients exhibited spasticity of hip adductors ($n = 24$; 89%), followed by knee extensors ($n = 23$; 85%) and ankle plantar flexors ($n = 21$; 78%; Table 1).

During the balance assessment, five individuals (20%) were not tested, as they were wheelchair users and could not perform the test, leaving only 21 patients to analyze. These patients generally exhibited a high risk of falls (median score = 17; $P = 0.03$; Table 1). Considerable variation in the type of gait assistance was found. Among the 27 patients, 8 (30%) walked without help, 3 (11%) required the assistance of a third party, 9 (33%) used a cane or crutch on one side, 2 (7%) used a walker and 5 (19%) required a wheelchair. As the majority of patients required a cane or crutch on one side, this variable was statistically significant ($P = 0.02$; Table 1). The remaining eight patients who did not require any gait assistance was evaluated, six of whom (75%) exhibited a considerable risk for falls (four with moderate risk and two with high risk; Table 1).

DISCUSSION

HTLV-1 is a sexually transmitted virus associated with different diseases, particularly HAM/TSP. HTLV-1 is endemic in Brazil, with ~2.5 million individuals infected. In the Amazon region, the state of Pará is considered one of the four states of Brazil with the highest prevalence of this infection. However, a large number of healthcare professionals are unaware of this disease. Thus, further studies are needed on diseases associated with HTLV-1, especially HAM/TSP, which is a neuro-inflammatory disorder that is etiologically associated with the virus. This disease has no cure yet, only palliative treatment to minimize the clinical symptoms.^{1,13}

The individuals with HTLV-1 treated at the Epidemiological Clinic of Endemic Diseases of the Tropical Medicine Sector of the Federal

University of Pará who did not fit all the criteria proposed by the WHO⁸ could not be considered as asymptomatic patients with HTLV-1, as the majority of them had some symptom related to the virus. Thus, the decision was made to use the classification criteria proposed by De Castro-Costa,⁸ which are simpler than those proposed by the WHO. De Castro-Costa⁸ proposed diagnostic levels to confirm the disease, such as definite, probable and possible. Such criteria have been widely used in clinical studies on HAM/TSP, as seen in the study by Nozuma *et al.*,¹⁴ who employed these criteria to screen patients, and in studies conducted by Starling *et al.*¹⁵ and Costa *et al.*¹⁶. In the present investigation, as in the aforementioned studies, the patients were screened using the criteria proposed by De Castro-Costa.⁸ However, only those with a definite diagnosis of HAM/TSP were included in the study.

Few studies in the literature have analyzed the neurological and functional manifestations of HAM/TSP.¹⁷ Previous studies only mention generalized disability. Studies performed by rehabilitation professionals remain scarce, especially those that include physiotherapists or that concern patients with HAM/TSP in the Amazon region.

The clinical analysis of patients with HAM/TSP is of considerable importance in determining the clinical profile of these patients and establishing possible rehabilitation strategies. Function scales have been used owing to their fast, easy administration.¹⁸ In the present study, the analysis of neurological symptoms was directed toward motor function owing to its clinical importance in relation to the progression of the disease, resulting in important changes with regard to functional independence and quality of life.⁷

Proximal weakness of lower limbs is one of the clinical characteristics of HAM/TSP.¹⁹ The Medical Research Council scale is commonly used to evaluate muscle strength in individuals infected with HTLV-1.¹⁶ In the present study, the patients exhibited muscle weakness, which was most evident in the proximal muscles of the lower limbs. This finding is in agreement with data reported in the literature and confirms the initial onset of muscle weakness in the proximal regions of lower limbs, which subsequently spreads to distal regions.^{4,20,21}

The hip adductors, knee extensors and ankle plantar flexors were evaluated for the assessment of spasticity, which are the most commonly tested muscles for the evaluation of spasticity in the lower limbs.^{11,22–24} No significant difference in spasticity was found between the right and left legs (Table 1). Moreover, patients with HAM/TSP exhibited a slight increase in muscle tone (median score of 1+), although with variation. The variation in spasticity demonstrates the tendency toward muscle weakness in the lower limbs.

Muscle weakness, particularly in the proximal region, associated with increased muscle tone can result in gait disorders.²⁵ When walking is no longer an automatic activity and requires the use of gait-assistance device, greater energy is spent for the same level of activity. Moreover, this leads to functional alterations that can increase the risk of falls.²⁶ Therefore, balance was analyzed in the present sample owing to the fact that this variable is closely linked to alterations in muscle strength and tone. The individuals studied had a significant risk of falls ($P=0.03$), despite the fact that all were in a rehabilitation program to improve their clinical status. Thus, both muscle weakness and spasticity are potential predictors of the progression of the disease, during which patients become dependent on walking aids.²⁵ According to Yamano and Sato,⁶ individuals with HAM/TSP initially require canes and, in advanced stages, become restricted to wheelchairs.

The patients with HAM/TSP evaluated in this study had a median score of 2 on the scale for the degree of aid required in locomotion

($P=0.02$) due to the use of a cane or crutch on one side. These findings are consistent with those reported by Franzoi and Araújo,¹⁷ who evaluated disability and walking performance in patients with HAM/TSP, the majority of whom used crutches.

The eight patients in the present study who did not use gait assistance had a high risk of falls. Thus, such individuals indeed needed gait assistance, but refused it owing to the stigmas associated with incapacitating diseases and the lack of physiotherapeutic interventions.

In conclusion, patients with HAM/TSP exhibited a similar clinical pattern in terms of muscle weakness and spasticity, both of which were concentrated in the proximal region of the lower limbs. Consequently, such patients have a high risk of falls and require walking aids. The identification of the main neurological problems in patients with HAM/TSP allows a more specific therapeutic intervention. The need for muscle strengthening, especially in the proximal region of the lower limbs, the control of muscle tone, and both static and dynamic balance training are needed to prevent falls and improve the quality of life of such patients.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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