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USING A NEW TOOL TO EVALUATE THE FUNCTIONAL CAPACITY OF PATIENTS WITH HTLV-1 ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

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ABSTRACT | HAM/TSP patients experience impaired functional capacity. The use of categorical scales to accurately describe motor ability in these patients has been questioned. **Aim:** To evaluate the functional capacity of HAM/TSP patients by using the individual tests comprising the GDLAM protocol. **Methods:** Cross-sectional study carried out in the CHTLV, Salvador, Brazil. Functional capacity was evaluated using the tests of the GDLAM protocol (timed 10-minute walk, getting up from a sitting position, rising from a prone position, getting up from a chair, and moving around the house). Functional classifications were made by comparing patient performance to that of uninfected control individuals. **Results:** Twenty-four HAM/TSP and 25 healthy individuals were enrolled. Only 75% HAM/TSP patients completed the GDLAM protocol. Six patients failed to perform the RPP test. Timed measurements were significantly higher in the HAM/TSP patients in comparison to uninfected controls. **Conclusion:** The use of alternative methods, such as the individual tests comprising the GDLAM protocol, may more accurately assess motor function in HAM/TSP patients.

Keywords: HTLV-1; HAM/TSP; functional capacity; activities of daily living.

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INTRODUCTION

Human T lymphotropic virus type-1 (HTLV-1) is endemic worldwide and it has been recently estimated that 10 million people harbor this virus[1].

HTLV-1 is etiologically linked to adult T cell leukemia (ATL)[2], tropical spastic paraparesis/HTLV-1-associated myelopathy (HAM/TSP)[3,4], uveitis[5] and infective dermatitis6. Furthermore, other diseases, such as polymyositis, sinusitis, bronchoalveolar pneumonia, keratoconjunctivitis sicca and bronchiectasis have been associated with HTLV-1 infection, indicating the multi-systemic character of this infection[1,7–9].

HAM/TSP is a rare disease, occurring in about 1-2% of HTLV-1 infected individuals, which mostly affects women in the 4th decade of life[10]. This disease is characterized by a slow and progressive demyelination of the spinal cord, mainly in the lower thoracic region, leading to motor abnormalities in the lower limbs[11]. Patients complain of weakness, back pain and urinary disorders, and on physical examination present spasticity, hyperreflexia with clonus and Babinski sign[11]. Studies have reported that these patients' limited mobility, loss of balance and muscle fatigue may lead to reduced functional capacity and impaired performance with respect to activities of daily living (ADL)[12–14].

The motor capacity of patients with HTLV-1 is usually assessed using categorical scales, such as the Expanded Disability Status Scale (EDSS)[15], the Osame Motor Dysfunction Scale (OMDS)[16], the Barthel Index[17] and the Functional Independence Measure (FIM)[12]. However, a recent study questioned the ability of categorical scales to accurately describe the functional capacity of patients with HAM/TSP[18]. These authors suggested that the timed 10 m walk test might be a more useful tool with which to evaluate the gait ability of patients with HAM/TSP, as well as to predict the development of motor disability in these patients.

The Latin America Group for Maturity (GDLAM) protocol, expressed in terms of the GDLAM index (GI), is another valuable tool to evaluate functional capacity[19,20]. Besides the timed 10-meter walk (10mTW), this protocol assesses other related functional abilities and may more accurately describe the functional capacity of patients suffering from myelopathy including HAM/TSP.

The aim of this study was to evaluate the functional capacity of patients with HAM/TSP by using the individual tests comprising the GDLAM protocol.

METHODS

Study design, location, and population

A cross-sectional study with a non-probabilistic sample was conducted between February and November 2014 at the HTLV Reference Center (CHTLV) of the Bahiana School of Medicine and Public Health (EBMSP) in Salvador, Bahia-Brazil. CHTLV is an outpatient clinic open to the public that provides inter-disciplinary care and services, including general medical treatment, laboratory diagnosis, psychological counseling and physical therapy. At present, 50% of the HTLV-1 infected patients seen at the clinic are being regularly followed. The majority of these patients are female and approximately 10% of all patients have been diagnosed with HAM/TSP.

Patients were sequentially selected in the context of a neurological consultation. Inclusion criteria were age ≥ 18 and ≤ 65 years and a definite diagnosis of HAM/TSP[21]. For comparison purposes, a control group of individuals who were not infected with HTLV (ELISA-negative) was recruited from the companions who accompanied patients during consultations.

Subjects were excluded if they had other causes of motor disability (e.g. stroke, trauma), used a wheelchair, presented evidence of co-infection, such as syphilis, hepatitis B and C and/or HIV, or had any other diseases that might lead to neurological deficiency (e.g. diabetes mellitus, multiple sclerosis, vitamin B12 deficiency and schistosomiasis). Following their neurological consultation, patients were invited to participate in this study and signed a term of informed consent. The EBMSP Institutional Research Board approved the present study under protocol number 768.968/2014.

Evaluations

The following variables were obtained: age, marital status, residence location, sex, initial symptoms related to HAM/TSP diagnosis, duration of disease, use of

walking aid and structured physical activity (motor physiotherapy, or other regular physical exercises) using a semi-structured questionnaire. Weight and height were also measured for all subjects in order to calculate body mass index (BMI).

Functional capacity was evaluated using the functional autonomy evaluation protocol previously described by GDLAM[19,20]. Briefly, the GDLAM protocol is composed of four tests measured in seconds by a digital chronograph (SW2018, Cronobio, Brazil): timed 10-minute walk (10mTW), getting up from a sitting position (GSP), rising from a prone position (RPP) and getting up from a chair and moving around the house (GCMH). Functional capacity (or GDLAM) index (GI) scores were calculated according to a previously described and functional classifications were made by comparing patient performance to that of uninfected control individuals[19,20].

The times obtained in the GDLAM protocol tests by the uninfected group were used as a reference parameter for comparison with the times obtained by patients with HAM/TSP. These times were categorized as very good (> p75), good (> p50 and ≤ p75), regular ((p25 and ≤ p50) and low (≤ p25)[19,20].

A single researcher (IRS) performed all functional capacity tests blindly for the neurological diagnosis.

Statistical analysis

Data are expressed as either means (±SD) or medians (25^{th} and 75^{th} percentiles) with respect to patient performance on the GDLAM test protocols. Categorical variables were described as proportions The Shapiro-Wilk test was used to test the normality of data distribution. Mann-Whitney non- parametric test was used to identify differences among groups. All data were analyzed using STATA v. 13 software, with $p<0.05$ considered significant.

RESULTS

A total of 49 individuals were enrolled, 24 of whom suffer from HAM/TSP, while 25 were HTLV-uninfected individuals. The mean (SD) age of HAM/TSP patients [48 (9.4) years] was significantly higher than uninfected subjects [39 (9.6) years; p=0.01]. Sociodemographic characteristics and BMI were similar between the two studied groups. Structured physical activity was more frequently reported by HAM/TSP patients (Table 1).

Table 1. Sociodemographic characteristics and BMI scores of studied individuals

	TSP/HAM N (%)	UC N (%)	P value
Age (years) *	48.0 (9.4)	39.0 (9.6)	0.010
Sex			
Male	8 (33.3)	5 (20)	0.232
Female	16 (66.7)	20 (80)	
Marital status			
Married /living with partner	11 (45.8)	11 (45.8)	0.563
Single/ widowed / divorced	13 (54.2)	13 (54.2)	
BMI (kg/m²)			
< 30.0	21 (87.5)	18 (72.0)	0.161
≥ 30.0	3 (12.5)	7 (28.0)	
Structured physical activity			
Yes	16 (66.7%)	5 (20%)	0.001
No	8 (33.3%)	20 (80%)	
Place of residence			
Salvador	16 (66.7)	21 (84.0)	0.141
Other city	8 (33.3)	4 (16.0)	

BMI: body mass index | UC: uninfected controls | * expressed as mean (SD)

Table 2 describes the HAM/TSP patients' clinical characteristics and timed performance results of the GDLAM test. Twelve (50%) patients required unilateral or bilateral support while walking. Weakness in the lower limbs was one of the most frequently observed early symptoms in 58% (14/24) of these patients, while urinary symptoms were present in 37.5% (9/24).

Table 2. Clinical and demographic characteristics and GDLAM test performance of 24 TSP/HAM patients

Number	Sex	Age	Duration (years)	Walking aid	Symptoms at time of onset	GDLAM test time (seconds)			
						10mTW	GSP	RPP	GCMH
1	F	22	5	US	WLL; PaLL	896.20	33.25	-	876
2	M	33	13	I	WLL; PaLL;	9.72	18.25	4.03	41.68
3	F	37	NA	BS	NP; NB	12.00	22.25	30.12	63.40
4	F	38	6	I	WLL; LBP	9.53	20.31	20.19	45.19
5	M	41	6	I	WLL	11.34	45.60	6.12	76.32
6	F	41	5	I	LBP; UI	9.22	14.65	3.28	40.15
7	M	44	6	US	WLL; UI	11.41	20.75	14.03	69.88
8	M	45	5	I	PaLL; UI	9.47	14.53	4.13	42.22
9	F	46	7	I	WLL	12.13	23.69	7.84	65.78
10	F	46	4	I	WLL; PaLL	13.09	31.00	29.00	73.00
11	M	46	7	US	WLL; UI	9.59	15.94	5.37	40.06
12	M	48	5	BS	UI	10.18	25.82	10.58	62.59
13	F	49	7	US	PaLL; PLL	12.57	17.97	-	69,5
14	F	50	3	I	WLL; PLL	16.03	13.50	14.00	69.72
15	F	51	5	BS	PaLL	50.90	26.78	-	228.22
16	F	52	5	I	WLL	7.73	13.12	4.60	43.90
17	F	53	8	I	spasticity and UI	23.88	25.63	-	143.72
18	M	53	6	I	PaLL	10.75	26.35	6.94	66.25
19	F	55	14	I	WLL	12.50	25.56	6.19	60.25
20	F	56	5	US	WLL; UI	17.28	32.81	-	160.28
21	F	59	12	BS	WLL; UV	32.03	39.59	-	139.50
22	F	59	17	US	PaLL; UI	11.50	18.90	8.97	69.66
23	M	60	9	BS	LBP; PaLL	30.43	23.75	14.41	116.09
24	F	62	6	US	WLL	15.91	19.69	15.69	84.78

F: Female; M: Male. NA: Not available; US: Unilateral Support; BS: Bilateral Support; I: Independent.
WLL: weakness in the lower limbs / PLL: pain in the lower limbs / PaLL: paresthesia of the lower limbs / UI: urinary incontinence / UV: uveitis / NB: neurogenic bladder / LBP: lower back pain / NP: neuropathic pain

Even patients with similar clinical conditions who did not require a walking aid exhibited markedly different performance parameters on the GDLAM test. For example, the 10mTW of patient 19 (12.5) was almost twice as long as that of patient 16 (7.73), similar to what was seen in these patients' GSP scores (13.12 vs. 25.56). Table 3 details the functional capacity classifications of the GDLAM protocol tests, in accordance with the quartiles of the control group. All HAM/TSP patients were classified as having low levels of autonomy.

Table 3. GDLAM test protocol results categorized according to performance (time measured in seconds) and quartile

	10mTW	GSP	RPP	GCMHC	GI
Very good	< 5.10	< 8.07	< 1.45	< 24.51	<17.93
Good	5.10 - 5.44	8.07 - 9.28	1.45 - 1.97	24.51 - 26.93	17.93 - 20.43
Regular	5.45 - 6.15	9.29 - 10.56	1.98 - 2.75	26.94 - 30.15	20.44 - 22.88
Low	> 6.15	> 10.56	> 2.75	> 30.15	> 22.88

Table 4 shows that the mean GDLAM tests timed functional assessment measurements of HAM/TSP patients were significantly higher than those of uninfected controls. Only 75% (18/24) patients with HAM/TSP successfully completed the GDLAM protocol and six patients failed to perform the RPP test.

Table 4. Mean GDLAM test performance according to clinical status

	TSP/HAM mean±SD	Control mean±SD	p value
10Mtw	15.61 ± 10.02	5.64 ± 0.76	<0.001
GSP	23.73 ± 8.21	9.37 ± 2.26	<0.001
RPP	11.41 ± 8.14	2.12 ± 0.76	<0.001
GCMHC	114.49 ± 168.41	28.03 ± 5.23	<0.001
GI	51.37 ± 14.99	20.76 ± 3.82	<0.001

Data are represented as mean ± standard deviation in seconds. 10mTW: timed 10 minute walk; GSP: getting up from a sitting position; RPP: rising from a prone position; GCMH: getting up from a chair and moving around the house; GI: GDLAM index. Teste de Mann-Whitney.

DISCUSSION

The present study found that individuals diagnosed with HAM/TSP present reduced functional capacity, which is consistent with previously published results[12,14,22]. In fact, HAM/TSP individuals exhibited low levels of performance on all the tests comprising the GDLAM protocol in comparison to control individuals. The low functional capacity observed in HAM/TSP individuals was expected, as myelopathy leads to significant motor limitations in these patients[23]. The average age of the uninfected control group in the present study was significantly younger than that of the HAM/TSP individuals, which could impact the assessment of functional capacity. Nevertheless, when comparing test results from a group of elderly individuals (mean age of 72 years) without neurological diseases from a previous study, these individuals still presented a better performance on the 10mTW and GSP tests compared to what was observed in the HAM/TSP individuals included herein[20].

Unlike other categorical scales typically used to monitor HAM/TSP patients, the GDLAM protocol objectively evaluates the time required to perform movements related to activities of daily living, allowing observers to obtain an overall perspective regarding the functional capacity of these patients[19,20]. The GSP test (getting up from a sitting position) requires strength in the lower limb musculature and the postural muscles, as well as coordination and balance. The RPP test (rising from a prone position), in addition to evaluating the capacity of the stabilizing muscles of the spine and the lower limbs, also incorporates upper limb musculature. Herein, six (25%) HAM/TSP patients were unable to perform the latter activity, indicating that upper limb movement could be also compromised in these individuals. It is known that even asymptomatic HTLV-1 individuals present neurological disorders, such as arm or leg weakness and hand or foot numbness, which can impact ADL[24,25].

The GCMH test (getting up from a chair and moving around the house), in addition to requiring the ability to walk and get up from a sitting position, also evaluates agility and proprioception. This test is of paramount importance to the independence of the individual since walking permits interaction with his/her surrounding environment[18].

GI comprises four tests within a single index. Thus, individuals with similar GI values could exhibit worse performance on one or more of the GDLAM tests. Therefore, we emphasize the relevance of use each of the test s of the protocols to more comprehensively evaluate functional capacity. We observed that patients with HAM/TSP walked at an average rate of 0.64m/s. It has been previously reported that, in functionally impaired individuals who walk at a speed lower than 0.7m/s, this value can be considered a cutoff useful for identifying an increased risk of falling, implying functional limitation[18]. Research has demonstrated that physical exercise can improve motor function capability, increase resistance, muscle strength, balance, and mobility[24,25], which may positively impact functional capacity and the quality of life in HAM/TSP patients.

The importance of maintaining a regular assessment regimen to detect subtle alterations in the functional state must be emphasized. In addition, objective evaluations can facilitate follow-up with respect to clinical and therapeutic evolution during the rehabilitation process, which aims to preserve, delay or even improve the profile of motor activity in these individuals.

We are aware that a variety of other factors can negatively affect functional capacities, such as advancing age, depression, level of physical activity and pain[26]. Although 67% of the individuals with HAM/TSP performed structured exercises or physiotherapy, all were classified as weak in comparison to the control group. We were, unfortunately, unable to evaluate levels of pain or depression, which should be investigated in future studies.

Taken together, the findings presented herein indicate that the individual tests comprising the GDLAM protocol hold the potential to more accurately assess motor function in HAM/TSP patients. These objective tests offer more precise information regarding functional capacity and may allow for tailored monitoring of patients during follow-up, as well as with respect to disease progression.

ETHICS STATEMENT

The present study was approved by the Research Ethics Committee under No. 768.968.

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COMPETING INTERESTS

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).Acknowledgments

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