

Major Article

Prevalence of Bowel Symptoms in Patients Infected with Human T-Lymphotropic type 1 Virus

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Abstract

Introduction: Bowel dysfunction is frequent in patients with spinal cord diseases, but little is known about the prevalence of bowel symptoms in human T-lymphotropic virus-(HTLV-1) infected individuals. The purpose of this study is to determine the frequency of bowel symptoms in HTLV-1 infected individuals and their correlation with the degree of neurologic disease. **Methods:** This is a cross-sectional study comparing the frequency of bowel symptoms in HTLV-1-infected individuals* and seronegative donors (controls). Patients answered a questionnaire, the Rome III Criteria was applied, and stool consistency was evaluated by the Bristol Stool Form Scale. The individuals were classified as HTLV-1 carriers, probable HTLV-1 myelopathy and definitive HTLV-1 associated myelopathy or tropical spastic paraparesis (definitive HAM / TSP)**. **Results:** We studied 72 HTLV-1 infected individuals and 72 controls with equal age and gender distribution. Constipation was the most frequent complaint, occurring in 38 % of HTLV-1 individuals and in 15 % of the controls. In comparison to the seronegative controls, the probability of constipation occurrence was approximately 18 times higher in definitive HAM / TSP patients. Straining, lumpy or hard stools, sensation of anorectal obstruction/blockage, fewer than 3 defecations per week, flatulence, soiling, evacuation pain, and bleeding were also more frequent in the HTLV-1 patients than in the controls. Moreover, bowel symptoms were more frequent in patients with definitive or probable HAM / TSP than in carriers. **Conclusions:** Bowel symptoms were more frequent in HTLV-1-infected patients than in seronegative controls and the frequency of bowel symptoms correlated with the severity of neurologic disease.

Keywords: Human T-lymphotropic virus 1. Constipation. Neurogenic Bowel.

INTRODUCTION

The HTLV-1 was initially identified in Japan in T cells of a patient with cutaneous lymphoma¹. It is estimated that about 10 million people worldwide are infected with HTLV-1². In Brazil, Salvador is the city with the highest prevalence of HTLV-1 cases

among blood donors and among the general population³. The most severe manifestations of the virus infection are HAM / TSP and adult T-cell leukemia / lymphoma (ATL), which affect about 1-5 % of infected individuals^{4,5}. However, other than myelopathy clinical and neurological manifestations in patients infected with HTLV-1 have been documented. These include dry mouth and eyes, periodontal disease, arthropathy, overactive bladder, and erectile dysfunction⁶. The pathogenesis of HTLV-1-associated diseases involves viral infection of immune cells leading to an exaggerated inflammatory response and tissue damage^{7,8}. HAM / TSP have been attributed to inflammation of the spinal cord, mainly at the level of the thoracic spine⁹.

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Patients with spinal cord diseases such as myelomeningocele, multiple sclerosis, and Parkinson's disease may have severe autonomic dysreflexia and neurogenic intestinal dysfunction characterized by constipation, incontinence, and altered visceral sensitivity¹⁰. Injury of the sacral roots can block the stimulation of afferent and efferent nerve fibers connecting the digestive apparatus and the brain, thereby causing motor and sensory dysfunction. This reduces the perception of the presence of the feces (solid or liquid) or gases in the rectum, leading to constipation, fecal incontinence, or both^{10,11}. Consequently, patients may develop abdominal pain, distension, fecal impaction, and hemorrhoids¹², which compromises physical and psychosocial status of the patients and reduces their quality of life¹³.

It is estimated that the prevalence of constipation in healthy adults in North America is about 14.8 %, being more prevalent in women and in people over 65 years (2.2 times higher)¹⁴. However, the occurrence of neurogenic bowel in individuals infected with HTLV-1 has been poorly studied. Constipation appeared the most frequent digestive tract symptom in HTLV-1 patients and two retrospective studies showed that it was present in 67 % and 78.2 % of patients with HAM / TSP^{15,16}. These studies did not address the frequency of other bowel symptoms and did not use a seronegative control group to allow a more rigorous comparison. The aim of the present study was to determine the prevalence of intestinal symptoms in HTLV-1-infected individuals and to evaluate the association of these symptoms in the context of various degrees of neurological disease.

METHODS

Site: The study was performed in the Multidisciplinary Clinic of HTLV in the Hospital Professor Edgard Santos of the Federal University of Bahia, in Salvador, Bahia, Brazil.

Population and study design: This is a cross-sectional study involving 72 HTLV-1-infected adult individuals and 72 seronegative controls with similar age (± 5 years) and gender ratio. The HTLV-1 infection was diagnosed by ELISA test, detecting antibodies (Cambridge Biotech, Worcester, MA) and confirmed by Western blot analysis (HTLV Blot 2.4, Genelabs, Science Park Drive, Singapore). The seronegative control group was recruited from blood banks of the Hematology and Haemotherapy Foundation of the State of Bahia (HEMOBA), Brazil. Patients with other myelopathies, diabetes mellitus, pregnancy, and history of other colorectal diseases were excluded.

Ethics: The study was approved by the Ethics Committee (Resolution No. 466/2012) and all patients participated voluntarily.

Data collection and definitions: A questionnaire aiming to obtain information on demographics and socio-economic profiles, as well as dietary and physical activity habits, was given to all participants. Data on beneficial against constipation water ingestion, physical activity, and intake of fruits and vegetables were categorized according to the following cutoffs: 7 or more glasses of water per day, physical activity 3 or more times per week, and daily intake of fruits and vegetables. A medical history

was taken and specific colorectal symptoms were recorded by the Rome III Criteria¹⁷ and Bristol Scale¹⁸ for stool consistency, which describes the appearance of feces in 7 types, as follows: types 1 and 2 dry stools, types 3 and 4 normal, type 5, 6, and 7 soft stools.

The HTLV-1-infected subjects were classified according the De Castro Costa criteria published in 2006¹⁹. Constipation was defined according to the Rome III criteria¹⁷. Fecal incontinence was defined as the loss of sphincter control or as the inability to contain the evacuation in socially inappropriate situations, resulting in the unexpected loss of gas, liquid, or solid stools²⁰.

Statistical analysis: Variables with normal distribution are summarized as mean and standard deviation. Categorical variables are presented in absolute and relative frequencies. The Student's t-test was used to compare means and the Fisher's exact test was used to compare proportions between groups. A single step multivariate logistic regression analysis was performed to evaluate the relationship between HTLV-1 status, stratified by the degree of neurologic impairment (main independent variable) and constipation (dependent variable), adjusted for lifestyle (physical activity, dietary habits and water intake). The significance level was set at 0.05. All analyses were performed with the Statistical Package for the Social Sciences, version 17.0.

RESULTS

The demographic, socio-economic, and general characteristics of the 2 groups are presented in **Table 1**. There was no difference regarding age, gender, and race between the groups. The income and education level were lower in the HTLV-1-infected individuals than in the control group. Constipation was the most common symptom, followed by hard stools, straining at defecation, pain, and flatulence. In the HTLV-1 group, all of these symptoms were present in higher frequency than in the seronegative controls. The frequency of less than 3 evacuations per week and of anorectal blocking were 5-fold and 3-fold higher, respectively, among HTLV-1-infected patients than in seronegative controls. Moreover, symptoms such as fecal incontinence, anorectal perception, and bleeding were at least 10-fold higher in HTLV-1 patients than in controls.

The frequency of type 2 and type 4 stools was higher among HTLV-1 patients than controls ($p < 0.05$). The frequency of type 2 stools was 26.8 % in the HTLV-1 patients versus 12.5 % in the control group and the frequency of type 4 stools was 26.8 % in HTLV-1 patients versus 45.8 % in controls. None of the participants reported type 7 stools.

The frequency of bowel symptoms according to the degree of neurologic disease is shown on **Table 2**. Subjects were classified as definitive HAM / TSP, probable HAM / TSP (all of them had neurogenic bladder, but no motor disability), and carriers. The bowel manifestations were more frequent in patients with definitive and probable HAM / TSP than in HTLV-1 carriers and controls. Most of the symptoms had a higher frequency in patients with definitive HAM / TSP, but straining at defecation was more frequent in the probable HAM / TSP group.

TABLE 1: Demographic, socioeconomic, and general characteristics of HTLV-1-infected patients and controls.

	HTLV-1 n=72	Controls n=72	P value
Age, years (mean ± SD)	49 ± 12	46 ± 10	0.13 ^a
Female gender (n %)	42 (58)	48 (67)	0.39 ^b
Monthly income (n %)			
No income	0 (0)	10 (14)	<0.01 ^b
< 2 minimum wage	46 (64)	34 (47)	
2 a 5 minimum wage	21 (29)	24 (33)	
5 a 10 minimum wage	4 (6)	3 (4)	
Education ^b (n %)			
Illiterate	5 (6.9)	2 (2.8)	<0.01 ^b
Elementary School	25 (34.7)	10 (14.1)	
High school	36 (43.9)	46 (64.8)	
Higher education	6 (8.3)	13 (18.3)	
Skin color ^b (n%)			
White	6 (8.5)	6 (8.5)	1.00 ^b
Brown	30 (42.3)	31 (43.7)	
Black	32 (45.1)	31 (43.7)	
Other	2 (2.8)	2 (2.8)	

HTLV-1: Human T-Lymphotropic Virus 1^aStudent's t test; ^bFisher's exact test; P < 0.05.

TABLE 2: Frequency of bowel symptoms in individuals with HTLV-1 and in controls according to the degree of neurological impairment.

Bowel symptoms	Definitive HAM/ TSP n = 16	Probable HAM/ TSP n = 14	HTLV-1 Carriers n = 42	Controls n = 72	P value ^a
	n (%)	n (%)	n (%)	n (%)	
Constipation ^c (n = 38)	11 (68.8)	8 (57.1)	8 (19.0)	11 (15.2)	< 0.01
Lumpy/hard stools* (n = 34)	11 (68.8)	7 (50.0)	5 (11.9)	11 (15.2)	< 0.01
Evacuatory frequency ^b (n = 14)	8 (50.0)	2 (14.3)	2 (4.8)	2 (2.7)	< 0.01
Anal bleeding (n = 10)	5 (31.3)	3 (21.4)	1 (2.4)	1 (1.4)	< 0.01
Straining at defecation ^c (n = 34)	6 (37.5)	8 (57.1)	9 (21.4)	11 (15.2)	< 0.01
Sensation obstruction/blockage ^c (n = 20)	7 (43.8)	4 (28.6)	4 (9.5)	5 (6.9)	< 0.01
Fecal soiling (n = 6)	3 (18.5)	2 (14.3)	1 (2.4)	0 (0)	< 0.01
Flatulence (n = 23)	8 (50.0)	5 (35.7)	6 (14.3)	4 (5.5)	< 0.01
Evacuatory pain (n = 23)	7 (43.8)	5 (35.7)	7 (16.7)	4 (5.5)	< 0.01

HTLV-1: Human T-Lymphotropic Virus 1; HAM/TSP: HTLV-1 associated myelopathy / tropical spastic paraparesis Rome III Criteria; ^aFisher's exact test; P value < 0.05; ^b< 3x / week.

To verify whether HTLV-1 infection was independently associated with constipation, a multivariate logistic regression analysis was performed, adjusted for water intake, physical activity, income, schooling, and fruit / vegetable consumption (Table 3). It was observed that definitive HAM / TSP individuals were approximately 18 times more likely to have constipation compared to seronegative controls (OR 18.00; 95 % CI 4.26-79.09); probable HAM / TSP were also significantly more likely to have constipation (OR 12.25; 95 % CI 2.84-52.86). However, HTLV-1 carrier status was not statistically associated with constipation.

DISCUSSION

HTLV-1 infection has been neglected mainly due to the low morbidity, as only 5 % of the patients develop HAM / TSP and ATL, the main diseases associated to this viral infection. However, about 20 % of patients who do not fulfill the criteria for HAM / TSP have a neurogenic bladder, mainly characterized by overactive symptoms⁷. Additionally, a large percentage of patients considered to be asymptomatic HTLV-1 carriers have other diseases or manifestations related to HTLV-1 including sicca syndrome, chronic periodontitis, uveitis, arthritis, and

TABLE 3: Multivariate logistic regression for prediction of constipation.

	Odds Ratio	95% CI	P value
HTLV-1 status (versus controls)			
Definitive HAM / TSP	18.00	4.26-79.09	< 0.001
Probable HAM / TSP	12.25	2.84-52.86	0.001
Carriers	1.47	0.48-4.53	0.494
Income (versus 5-10 minimum wage)			
No income	2.28	0.16-32.79	0.546
< 2 minimum wage	1.03	0.11-9.33	0.976
2-5 minimum wage	1.03	0.11-9.81	0.981
Education (versus higher education)			
Illiterate	2.00	0.18-22.40	0.572
Elementary School	1.31	0.23-7.29	0.758
High school	1.77	0.34-9.11	0.496
Physical activity practice* (yes versus no)	0.89	0.30-2.67	0.839
Daily intake of fruits and vegetables (yes versus no)	0.52	0.21-1.32	0.170
Low water intake** (yes versus no)	1.00	0.40-2.55	0.992

HTLV-1: Human T-Lymphotropic Virus 1; HAM/TSP: HTLV-1 associated myelopathy / tropical spastic paraparesis; HC: HTLV-1 carries 95 % CI: 95 % confidence interval; P value < 0.05; * $\geq 3x$ / week; ** < 7 glasses a day.

erectile dysfunction^{6,21}. In the present study, we show that the frequency of bowel symptoms, such as constipation, bleeding, sensation of obstruction / anorectal block, hard stools, low evacuation frequency, and straining defecation was higher in HTLV-1 infected individuals categorized in definitive HAM / TSP and probable HAM / TSP groups than in HTLV-1 carriers and seronegative controls. Moreover, the frequency of bowel symptoms increased along with the severity of the neurologic disease.

While in the last 15 years, it became clear that HTLV-1-infected individuals even without myelopathy had urinary symptoms and erectile dysfunction^{22,23}; no studies have evaluated intestinal complaints in such patients. In patients with HAM / TSP, the frequency of constipation was reported to be greater than 60 %^{15,16}. It is known that intestinal dysfunction is common in patients with spinal cord injuries²⁴. Here, we show that bowel symptoms were more frequent in HTLV-1 patients with HAM / TSP and probable HAM / TSP than in HTLV-1 carriers and seronegative controls. HTLV-1 carriers behaved similarly to seronegative controls regarding intestinal symptoms. Older age and female gender are factors commonly associated with intestinal complaints, but the participants in our study were age and gender matched.

Constipation was the most frequent complaint in both HTLV-1 patients and control group. Nevertheless, constipation was still significantly more common among the patients than in the control group. The differences in the frequency of other important bowel symptoms were even more significant. For example, pain and sensation of obstruction were 4 times more frequent in HTLV-1 patients than in the controls. Anorectal

perception, fecal incontinency, and bleeding were 10 times more frequent in the HTLV-1-infected individuals than in seronegative controls.

Intestinal dysfunctions were more frequent in patients with HAM / TSP and patients with neurogenic bladder than in HTLV-1 carriers, indicating a relationship between bowel symptoms and evidence of spinal cord injury. We have previously shown that the frequency of other symptoms related to neurogenic injury in HTLV-1-infected patients, such as erectile dysfunction, was higher in patients with probable HAM / TSP and definitive HAM / TSP²³. Moreover, the severity of erectile dysfunction measured by the international index of erectile function was directly associated with the severity of neurologic involvement. In the present study, the frequency of bowel symptoms was similar among patients with definitive HAM / TSP and those with only neurogenic bladder. It is likely that the proximity of the neural branches that control the bladder and those related to anorectal function can lead to a high coexistence of bladder and bowel symptoms²⁴. This underscores the importance of addressing both bowel and bladder dysfunction in such population.

We recognize that the present study has some limitations. For instance, the difference observed in the income and education levels between the groups may be seen as confounding factors, as these variables may influence dietary habits, the occurrence of allergic and inflammatory bowel diseases, and the frequency of helminthic and protozoa intestinal infections, conditions that may lead to bowel dysfunction. However, previous data in the literature and some observations shown here argue against the influence of these variables in the obtained results. Constipation

was the more frequent complaint among HTLV-1 patients, but this symptom is also observed in high frequency in individuals living in developed countries such as the United States²⁵. We did not evaluate the occurrence of allergic and bowel inflammatory diseases, but there is evidence that allergic and bowel autoimmune diseases are inversely correlated with the income²⁶. In regards to helminths and protozoa intestinal infections, we have previously shown that with the exception of *Strongyloides stercoralis* and *Schistosoma mansoni*, the frequency of entero parasites in HTLV-1 patients is similar to that observed in seronegative controls with similar income²⁷. Moreover, due to the well-documented association between strongyloidiasis and HTLV-1 infection, stool examination is performed upon admission of all patients in the HTLV-1 clinic and provided treatment. Because of this policy, a low frequency of intestinal parasites is now observed in our cohort. Indeed, while in our cohort we have not observed differences in income and education levels between HTLV-1 carriers and patients with HAM / TSP, bowel manifestations were highly associated with neurologic disease.

In conclusion, constipation, straining, lumpy or hard stools, sensation of anorectal obstruction/blockage, fewer than 3 defecations per week, flatulence, soiling, evacuation pain, and bleeding are more frequent in HTLV-1 patients than in seronegative controls. The prevalence of bowel symptoms was also higher in patients with probable and definitive HAM / TSP than in HTLV-1 carriers, indicating that neurologic damage to the spinal cord plays an important role in bowel symptoms among patients with HTLV-1 infection.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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