

RESEARCH GROUP IN RETROVIRUS AND ASSOCIATED DISEASES

PROVIRAL LOAD OF HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) AND COMORBIDITIES IN ASYMPTOMATIC CARRIERS

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Abstract

This study aimed to describe comorbidities and symptoms of asymptomatic HTLV-1-infected patients according to the proviral load. Medical records were revised and patients categorized in high and low proviral load groups: >5% and <5% -infected cells, respectively. Frequency of symptoms was quantified. A total of 64 patients were evaluated. Twenty three (36%) patients had high proviral load. All patients had clinical abnormalities reported in the medical records. The most frequently comorbidities were hypertension (37.5%) and depression (25%) and the most frequent symptoms were neurological (82.8%) and ophthalmologic (65.6%). There were no differences in the frequencies of clinical manifestations in patients with low and high proviral load, except for urinary retention, that was more prevalent in the group with high proviral (34.8%). In summary, patients infected with HTLV-1 asymptomatic have a wide spectrum of clinical abnormalities and should be closely followed in order to identify the development of HTLV-1-associated diseases.

Keywords: Human T-cell lymphotropic virus type 1; Proviral load; Asymptomatic carriers.

INTRODUCTION

The human T-cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus isolated⁽¹⁾ and later was associated with the development of adult T-cell leuke-

mia/lymphoma (ATLL),⁽²⁾ HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)^(3,4) and HTLV-1 uveitis (HAU).⁽⁵⁾ There are 15 to 20 million people are infected with HTLV-1 in the world, mainly in the southeast of Japan and in the poor areas of the Caribbean, Africa and Latin America.⁽⁶⁾ Brazil has the largest absolute number of individuals infected with HTLV-1 in the world, however the prevalence of infection varies between regions.^(6,7) The highest prevalence is observed in Salvador, Bahia, where about 2% of the population (\approx 50,000 people) is infected.⁽⁸⁾

It has been reported that only 5% of infected individuals develop one of the diseases associated with the virus, however, a growing number of evidence indicates a higher prevalence of paresthesias, urinary symptoms, arthralgia, erectile dysfunction and gingivitis in individuals infected asymptomatic compared to uninfected individuals.^(9,10) To date, there is no biomarker associated with evolution to associated-HTLV-1 diseases. The proviral load is the proviral DNA integrated into the host cell genome and a proviral load higher than 5% of the infected cells has been described as the best cutoff value to discriminate asymptomatic individuals from patients with HAM /TSP.⁽¹¹⁾ A high proviral load was also associated with the presence of keratoconjunctivitis sicca in patients infected by HTLV.⁽¹²⁾ The aim of this study was to describe comorbidities and symptoms of asymptomatic HTLV-1-infected patients according to the proviral load.

METHODS

This was a retrospective cross-sectional study involving patients infected with HTLV-1 followed at the Integrative Center for HTLV (CHTLV) at Bahiana School of Medicine and Public Health (EBMSP) in Salvador, Brazil. Patients were included if they had a positive serology for HTLV-1 confirmed by Western blot, proviral load data available, and were regularly followed at the CHTLV in the period of 2008-2011. Asymptomatic individuals were defined as those without diagnostic criteria for diseases classically associated with HTLV-1: ATLL, HAM / TSP, HAU. Patients whose medical records did not permit the completion of at least 50% of the questionnaire were excluded. Medical records were analyzed according to a standard questionnaire containing demographic data, comorbidities and signs and symptoms. Patients were categorized according to the levels of proviral load (above or equal to 5% of infected cells) (11) and the frequency of clinic abnormalities were quantified. Statistically significant differences were identified using the chi-square test or Fisher's exact test and the nonparametric Mann-Whitney U test using SPSS®. The study was approved by the Institutional Research Board of EBMSP.

RESULTS

Sixty four out of 71 asymptomatic patients with proviral load data were included in the study. Among the 64 patients studied, 47 (73.4%) were female, 40 (62.5%) were from Salvador, Bahia. All patients had clinical abnormalities reported in the medical records. The most frequent symptoms were neurological (82.8%), followed by urological (62.5%) and ophthalmological (65.6%) complaints. Arterial hypertension (37.5%), depression (25%) and type 2 diabetes mellitus (18.8%) were the most frequent comorbidities. High proviral load (> 5% of cells infected) was found in 23 patients (36%). No significant differences were observed between the frequencies of clinical manifestations and comorbidities of patients with low and high proviral load for neurological, urological, ophthalmological and dermatological abnormalities. The exception was urinary retention, that was more frequent in the group with high proviral (34.8%) compared to the group with low proviral load (7.3%) ($p = 0.012$).

DISCUSSION

All HTLV-1-infected asymptomatic patients had clinical abnormalities described in the medical records and one third of them had a proviral load higher than 5% of the infected cells, which is considered the best cutoff value to distinguish asymptomatic individuals from patients with HAM/TSP.⁽¹¹⁾ However, no statistical differences were observed in the frequency of symptoms or comorbidities between groups with high and low proviral load, except for urinary retention, more frequent among patients with high proviral load. Urinary retention is a finding of urodynamic study and indicates a high post-voiding residue, resulting from the partial bladder emptying. The HAM/TSP is a neurological syndrome characterized by paraparesis, manifested clinically by progressive weakness, hyperreflexia and sensory symptoms, like paresthesias in lower limbs and back pain.⁽⁴⁾ Urinary and sexual abnormalities may be early manifestations of this syndrome. The most frequent urinary symptoms are bladder fullness, urinary retention, urinary incontinence, pollakiuria and urinary tract infections.⁽¹⁰⁾

In this study we observed a higher frequency of urinary retention and bladder fullness in individuals with high proviral load. It is believed that the neurological lesion HAM/TSP is initiated by an inflammatory process caused by the virus infection of astrocytes and endothelial cells that comprise the blood brain barrier. The functional alterations of the barrier allow the passage of infected lymphocytes into the central nervous system. Then, there would be a degenerative process with progressive destruction of the white substance and little involvement of the gray substance, par-

ticularly in corticospinal tract.⁽¹³⁾ HTLV-1 preferentially infects CD4⁺ T lymphocytes and induces a spontaneous proliferation of these cells, followed by the increase of inflammatory cytokines like interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL -6).^(14,15) The mechanism of spinal cord injury is still unclear, but three hypotheses are accepted: i) apoptosis of glial cells infected induced by specific CD8⁺ T cells, ii) cross-reaction between self-antigens and viral antigens leading to destruction of cells of the nervous system, and finally iii) damage caused by high levels of inflammatory cytokines produced by CD4⁺ and CD8⁺ T-cells resulting in inflammation and degenerative injury.¹⁶ Since the high proviral load is related to the risk of HAM/TSP, it is possible that individuals infected by HTLV-1 without any HTLV-1-related diseases with high proviral load are those that will develop the HAM/TSP. This study is limited by its cross-sectional design and the fact that the implications of a high HTLV-1 proviral load on asymptomatic individuals in the development of HTLV-1-associated diseases may not be addressed. Additional longitudinal studies should be carried out to further evaluate this question.

CONCLUSION

HTLV-1-infected asymptomatic individuals without HTLV-1-associated diseases have a wide spectrum of clinical abnormalities, and the frequency of urinary retention was higher in those with high proviral load. Patients with high proviral load should be followed more frequently in order to assess the development of diseases associated with HTLV.

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