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High HTLV-1 proviral load, a marker for HTLV-1-associated myelopathy/tropical spastic paraparesis, is also detected in patients with infective dermatitis associated with HTLV-1

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Salvador (BA, Brazil) is an endemic area for human T-cell lymphotrophic virus type 1 (HTLV-1). The overall prevalence of HTLV-1 infection in the general population has been estimated to be 1.76%. HTLV-1 carriers may develop a variety of diseases such as adult T-cell leukemia/lymphoma, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infective dermatitis associated with HTLV-1 (IDH). IDH is a chronic and severe form of childhood exudative and infective dermatitis involving mainly the scalp, neck and ears. It has recently been observed that 30% of patients with IDH develop juvenile HAM/TSP. The replication of HTLV-1 has been reported to be greater in adult HAM/TSP patients than in asymptomatic HTLV-1 carriers. In the current study, the proviral load of 28 children and adolescents with IDH not associated with HAM/TSP was determined and the results were compared to those obtained in 28 HTLV-1 adult carriers and 28 adult patients with HAM/TSP. The proviral load in IDH patients was similar to that of patients with HAM/TSP and much higher than that found in HTLV-1 carriers. The high levels of proviral load in IDH patients were not associated with age, duration of illness, duration of breast-feeding, or activity status of the skin disease. Since proviral load is associated with neurological disability, these data support the view that IDH patients are at high risk of developing HAM/TSP.

Key words: Infective dermatitis associated with HTLV-1; HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1 proviral loads

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Introduction

Salvador (BA, Brazil) is an endemic area for human T-cell lymphotrophic virus type 1 (HTLV-1). The overall prevalence of HTLV-1 infection in the general population has been estimated to be 1.76% (1). HTLV-1 carriers may develop a variety of diseases such as adult T-cell leukemia/lymphoma (ATL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infective dermatitis associated with HTLV-1 (IDH). While IDH is a childhood disease, ATL and

HAM/TSP are considered to be adult diseases. IDH is a chronic and severe form of exudative and infective childhood dermatitis involving mainly the scalp, neck and ears, and consisting of a generalized papular rash, nasal discharge and crusting of the nostrils. The disease responds immediately to antibiotic or sulfamethoxazole-trimethoprim therapy and, conversely, relapses immediately once treatment is withdrawn (2,3).

It has recently been observed that 30% of patients with IDH develop juvenile HAM/TSP (4) and this skin manifestation probably represents a risk factor for the development of ATL (5,6).

Maloney et al. (7) studied 28 asymptomatic infected children and observed an elevated viral load in only 2 of them, one of whom developed IDH. There is only 1 case of IDH in children in which HTLV-1 proviral load was determined. This case had a coinfection with *Strongyloides stercoralis* and presented a high proviral load. This same finding has been described in adult carriers with strongyloidiasis (8).

In a study evaluating seven carrier children with seborrheic dermatitis compared with 19 carrier children without seborrheic dermatitis, a higher mean proviral load [7.5 copies/100,000 peripheral blood mononuclear cells (PBMCs)] was found in children with seborrheic dermatitis compared to children without seborrheic dermatitis (3.1 copies/100,000 PBMCs) (9). Recently, it was reported that the proviral load in HTLV-1-infected children with a type of eczema not considered to be IDH increased to a median of 9220 copies/100,000 PBMCs at equilibrium, which was significantly higher than the median proviral load found in carrier children without eczema or in adult carriers (10).

In the current study, the proviral load of 28 children and adolescents with IDH not associated with HAM/TSP was determined and the results were compared to those obtained in 28 HTLV-1 adult carriers and 28 adult patients with HAM/TSP.

Material and Methods

The IDH patients were diagnosed and followed up at the Dermatology clinic and referred to the Neuropediatric clinic of Complexo Hospitalar Universitário Prof. Edgard Santos, Universidade Federal da Bahia. The HAM/TSP patients were being followed up at the HTLV-1 clinic of the same hospital. The HTLV-1 carriers were selected consecutively from blood bank donors. The group of IDH patients consisted of 18 girls and 10 boys, all of African descendent. Patient age ranged from 2 to 16 years (mean: 10.8 ± 3.6 years) at the time of blood sampling. Duration of breast-feeding ranged from 0.1 to 4.9 years (mean: 2 ± 1.3 years) and the duration of the disease ranged from 0.3 to 15 years (mean: 8.6 ± 3.9 years). Twenty-four patients (85.7%) had active disease at the time of blood sampling, while the remaining four (14.3%) were in remission. Neurological examination failed to reveal HAM/TSP in any of the 28 IDH patients. The presence of HTLV-1/II antibodies was investigated by ELISA and confirmed by Western blot (HTLV blot 2.4, Genelab, Singapore). All patients were HIV-negative. Stool examinations were performed in all patients at the time of blood sampling. The diagnosis of IDH was made according to established criteria (2,3). The DNA was extracted from 10^6 PBMCs using a phenol/chloroform procedure (11). HTLV-1 proviral load was determined using real-time TaqMan PCR (11). The GraphPad Prism 3.03 software (USA) was applied for statistical analysis and P values <0.05 were considered to be statistically significant. The Mann-Whitney U-test was used to compare data. The study was approved by the Ethics Committee of the Complexo Hospitalar Universitário Prof. Edgard Santos, Universidade Federal da Bahia, and the parents or legal guardians of the participants gave written informed consent at the time of blood sampling.

Results

The proviral loads of IDH patients were much higher (Figure 1), with a median of 160.480 (range: 26.382-965.825) copies per 10^6 PBMCs compared to the HTLV-1 adult carriers, who presented a median of 25.337 (range: 19.0-133.251) copies per 10^6 PBMCs ($P < 0.0001$). No statistically significant difference in proviral load was found between the IDH and the adult HAM/TSP patients. The proviral loads of adult HAM/TSP patients were also higher than those found in carriers, with a median of 127.055 (range: 35.0-691.862) copies per 10^6 PBMCs ($P = 0.0017$). No statistically significant associations were observed between proviral loads and age, duration of breast-feeding, duration of IDH and the status of disease activity (Table 1). Examination of stool specimens detected *Strongyloides stercoralis* in only 1 patient whose proviral load was 299.680 copies per 10^6 PBMCs.

Discussion

Many studies have emphasized the importance of evaluating HTLV-1 proviral load in individuals at a higher risk for HAM/TSP (12). As previously shown, patients with IDH have a high risk of developing HAM/TSP (4,6). The replication of HTLV-1 has been reported to be greater in adult HAM/TSP patients than in asymptomatic HTLV-1 carriers (12). In the present study, proviral load was found to be

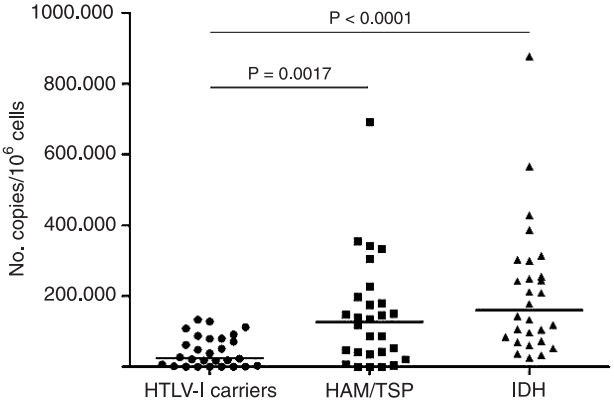

Figure 1. Proviral loads of IDH patients, HTLV-1 carriers and HAM/TSP patients. Proviral load was assessed in PBMCs from 28 IDH patients, 28 HTLV-1 carriers and 28 HAM/TSP patients. Proviral load was significantly higher in IDH patients compared to HTLV-1 carriers ($P < 0.0001$, Mann-Whitney U-test). IDH = infective dermatitis associated with HTLV-1; HTLV-1 = human T-cell lymphotrophic virus type 1; HAM/TSP = HTLV-1-associated myelopathy/tropical spastic paraparesis.

Table 1. Proviral loads of infective dermatitis associated with human T-cell lymphotrophic virus type 1 (HTLV-1) patients.

	No. of IDH cases	Proviral load (median)	Range
Age at the time of blood sampling			
≤10 years	13	118.519	32.983-566.368
>10 years	15	206.262	26.382-965.825
Duration of breast-feeding*			
≤1.0 year	7	70.222	26.382-255.070
>1.0 year	19	206.262	32.983-965.825
Duration of disease**			
≤10 years	15	177.778	32.983-965.825
>10 years	12	138.283	26.382-386.874
Status of activity of disease			
In activity	24	138.283	26.382-965.825
In remission	4	245.914	85.259-428.166

IDH = infective dermatitis associated with HTLV-1. *No information was available about 2 patients: one was an orphan and the other was not breast-fed and was infected through blood transfusion. **This information was missing for the orphan patient. There were no statistical differences between subgroups for age, duration of breast feeding, duration of disease, or status of disease (Mann-Whitney U-test).

higher in IDH patients than in HTLV-1 carriers. The high proviral load in IDH was not associated with age, duration of illness, duration of breast-feeding, or activity status of the skin disease. Therefore, it is likely that patients who have high proviral loads were already infected with a high viral load or are genetically susceptible.

The main finding of the present study was the fact that there was no statistically significant difference between viral replication in IDH and that observed in adulthood HAM/TSP. In addition, the proviral load detected in the IDH patients was much higher than that observed in HTLV-1-infected children with eczema (10). A high proviral load has been demonstrated to represent a risk factor for the development of adult HAM/TSP (13). Thus, a high proviral load in IDH may probably predispose (in addition to other factors) to the development of juvenile HAM/TSP, at least in Bahia, Brazil, where 30% of the IDH patients develop myelopathy.

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